Interim Session — Seattle, Washington
November 25-26, 1956

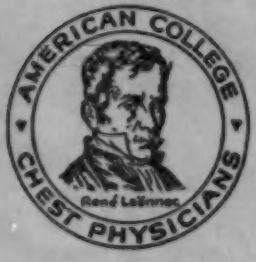
VOLUME XXX NUMBER 4

DISEASES

of the

CHEST

OFFICIAL PUBLICATION



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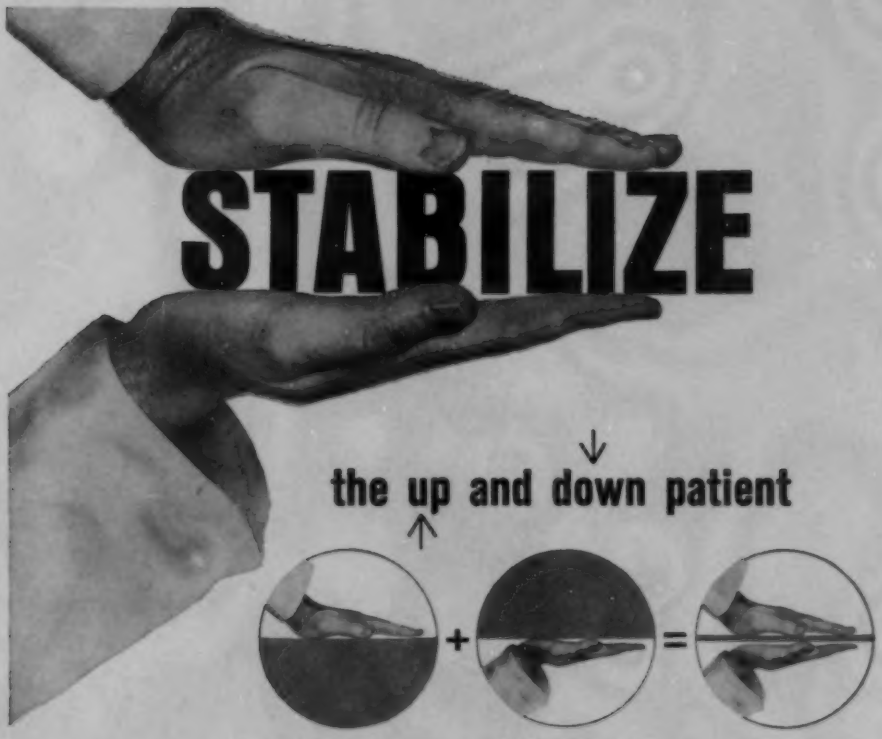

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1. Arnoff, B.: Personal communication. 2. Lazarte, J. A., and Petersen, M. C.: Personal communication.

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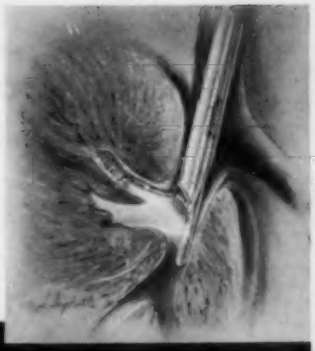

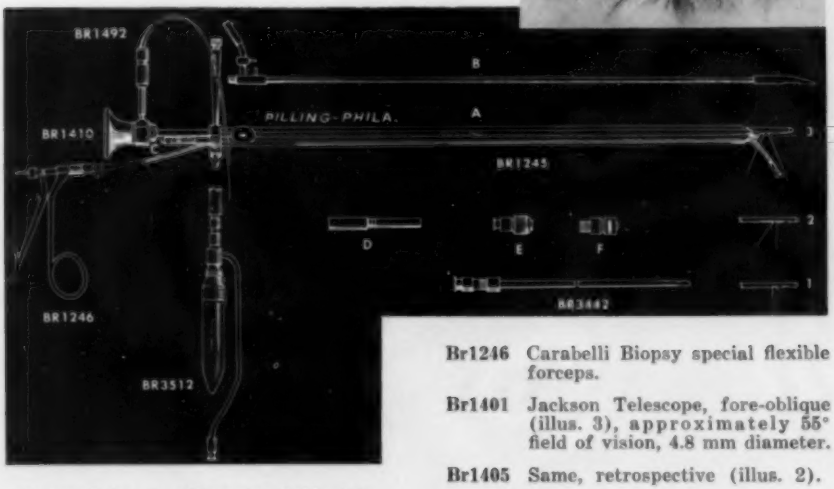

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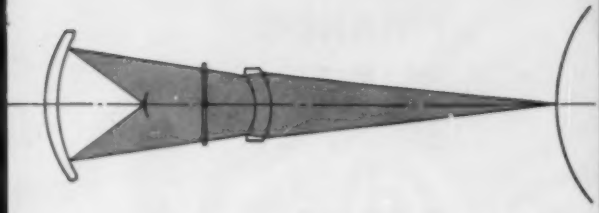

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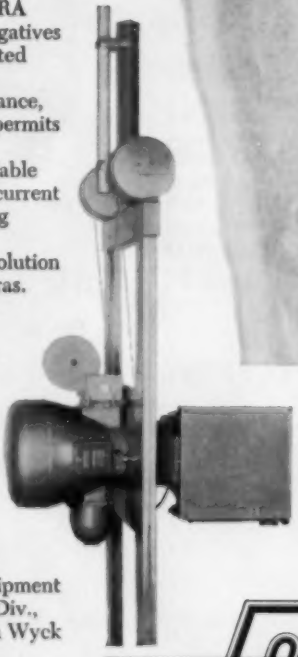

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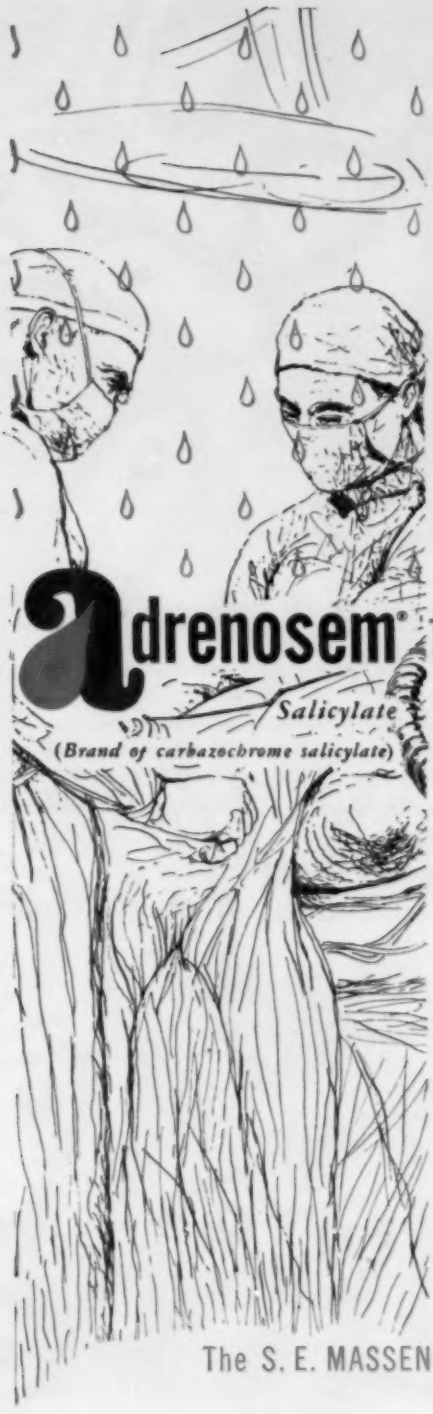

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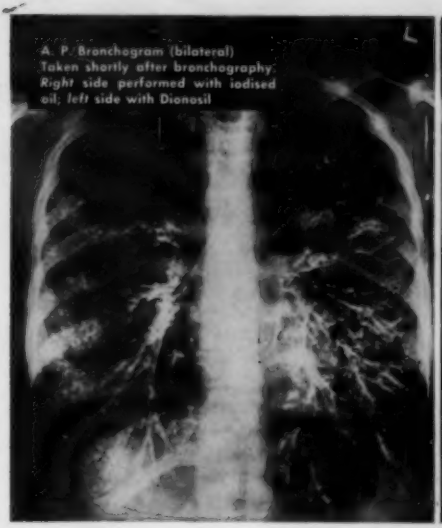
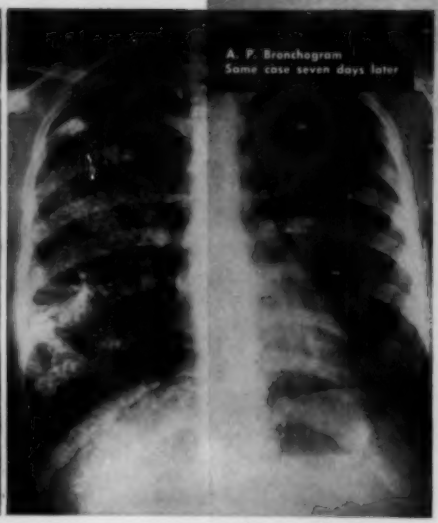


A. P. Bronchogram (bilateral)
Taken shortly after bronchography: *Right* side performed with iodised oil; *left* side with Dionosil



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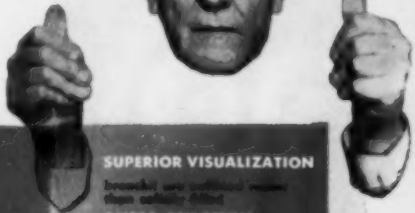

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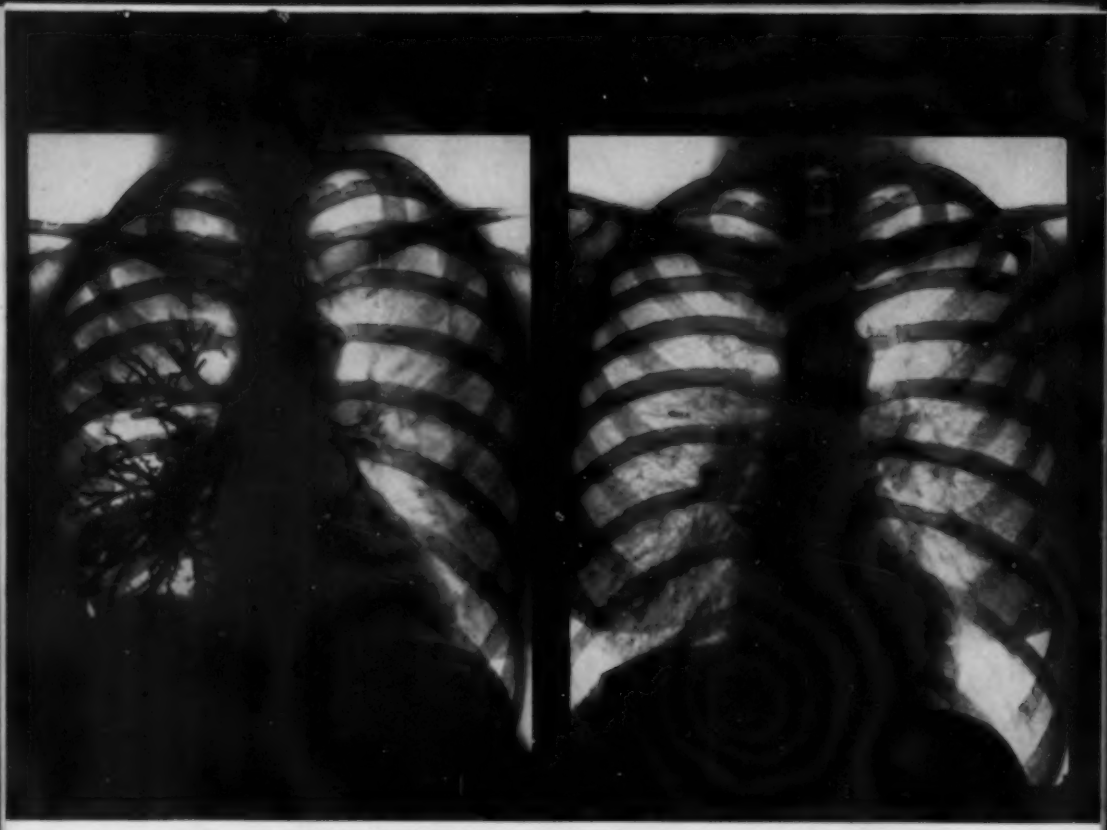

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Chest x-ray three days after bronchogram. Note clearing of VISCIODOL and fluid level in right hilar cavity.

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1. Burrascano, J. J.: Sea View Hosp. Bull. *15*:149 (July) 1955.

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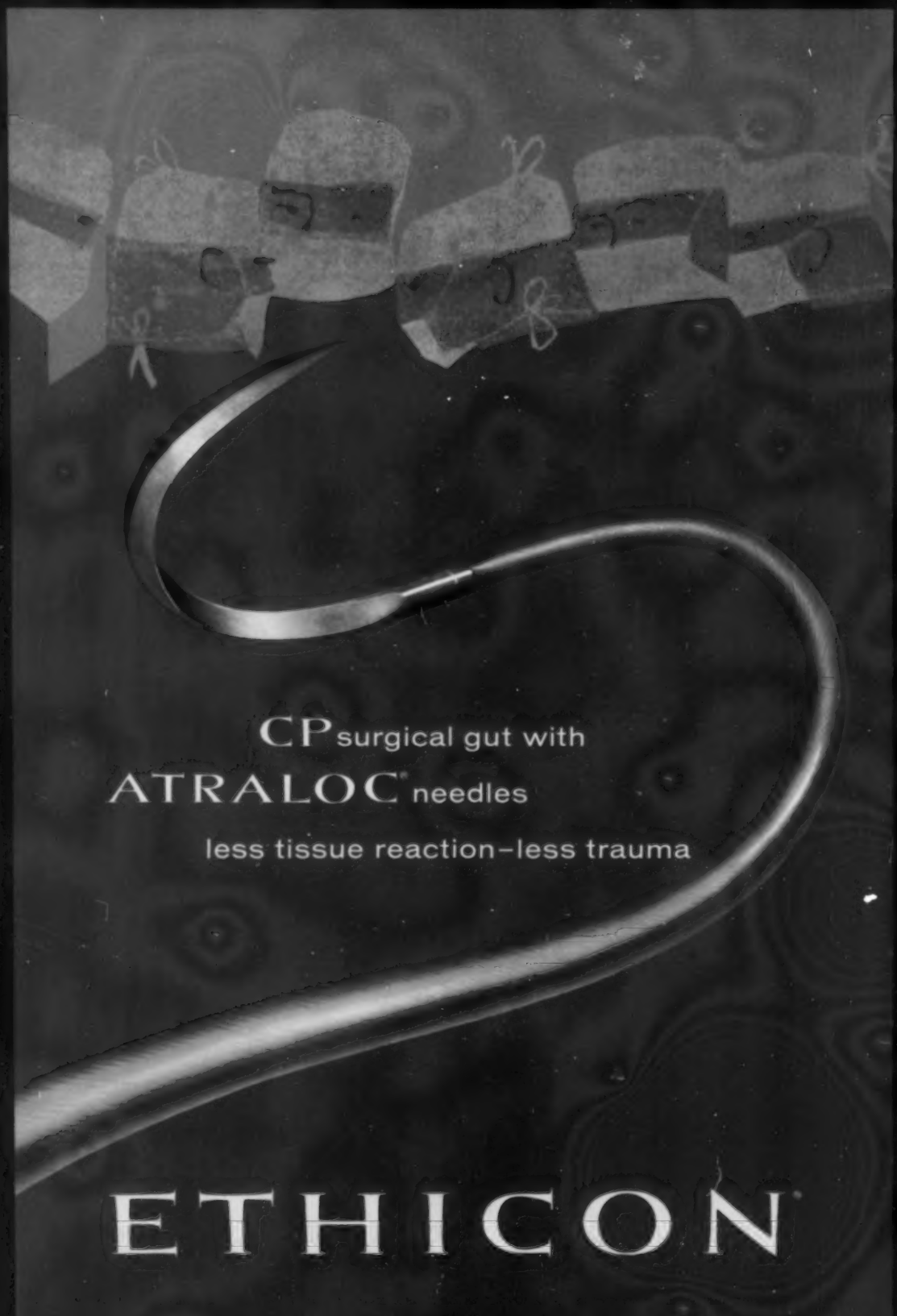
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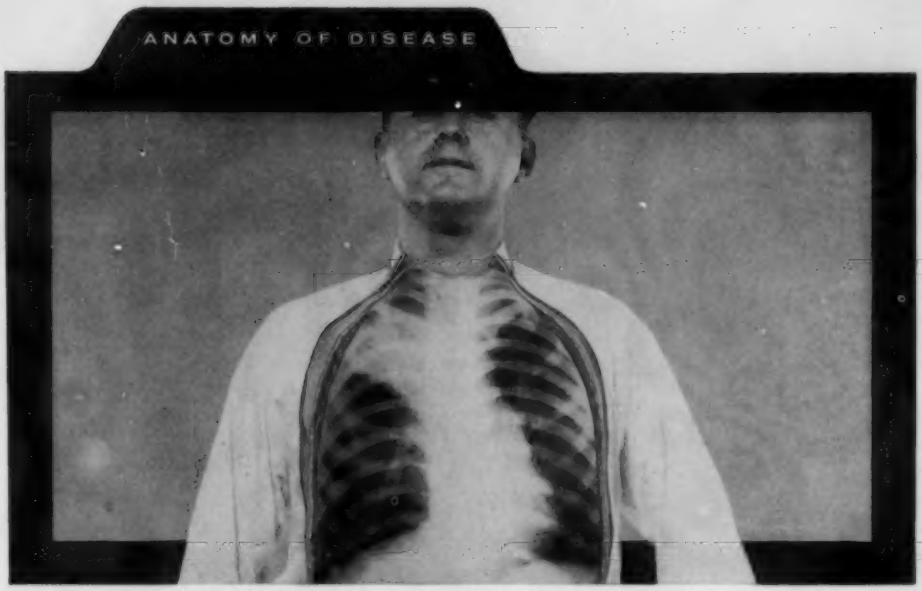

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1. Camerata, S. J.; Jacobs, H. J., and Affeldt, J. E.: Read Before The Southern California Chapter of The American College of Surgeons, Palm Springs, Calif., January 23, 1953.

2. Miller, W. F.: New England J. Med. 251: 889, 1955.

3. Limber, C. R.; Reiser, H. G.; Roettig, L. C., and Curtis, G. M.: J.A.M.A. 149: 816, 1952.

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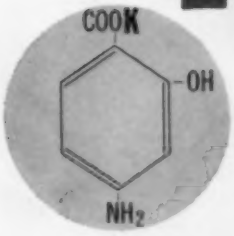

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1. *Molthan, L., Cohen, R. V., and Zarafonetis, C. J. D.: Clinical use of potassium para-aminosalicylate (KPAS). Am. Rev. of Tuberc. and Pulmon. Dis. 71:220 (Feb.) 1955.*

2. *Cohen, R. V., Molthan, L., and Zarafonetis, C. J. D.: Clinical Studies of Various Forms of PAS (with special reference to plasma concentrations). Read before the American Trudeau Society, Annual Meeting, Milwaukee, Wisconsin, May 23-27, 1955.*

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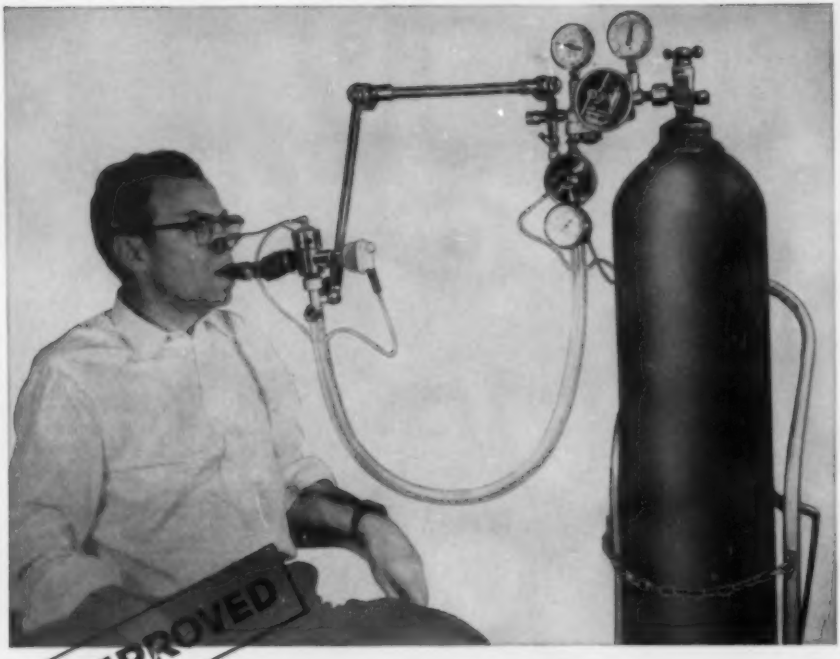

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Pennsylvania Chapter, Atlantic City, New Jersey, October 24, 1956
Potomac and Southern Chapters (Joint Meeting) Washington, D. C.
November 11-12, 1956

DISEASES of the CHEST

VOLUME XXX OCTOBER, 1956 NUMBER 4

Direct Spatial Vectorcardiography

Clinical Application

BERTRAM JOHN ALLENSTEIN, M.D., F.C.C.P.

Los Angeles, California

Electrocardiography may be defined as the science which deals with the study of electrical forces in heart muscle. Our present methods of recording this electrical activity give us average potentials possessing magnitude and sense and, in effect, portray a two-dimensional view of this activity. However, this electrical activity occurs in three dimensions; therefore, fundamental electrocardiography requires a study of the magnitude, sense, and direction of the electrical forces. To achieve a three-dimensional comprehension many methods of computation have been devised and many *leads* have been advocated, including three standard limb leads, three unipolar leads, precordial leads, esophageal leads, and back leads, so that at present approximately 110 different leads have been advocated in this effort to better picture the electrical activity.

Vectorcardiography is actually basic, fundamental electrocardiography and in three dimensions. It may be direct or indirect. The indirect methods[1] require detailed measurements and calculations with the electrocardiogram as the starting point. Direct spatial vectorcardiography permits the visualization of the termini of the instantaneous vectors by the cathode-ray oscilloscope. In effect, the electrical potential is viewed in three dimensions. This discussion will be limited to a brief summary of the clinical use of direct spatial vectorcardiography, using the cube electrode placement of Duchosal-Sulzer as modified by Grishman[2] and his group. More recently we have also utilized the Kimura electrode placement.

Method

When describing the spatial orientation of the vectors, we describe the vector as in a solid cube, referring to the patient's left and right, anterior and posterior, inferior and superior octants (Fig. 1A). The E point represents zero potential. Electrodes are placed at the level of vertebral body L-1 at the left posterior axillary line and at the right posterior and anterior axillary line. The fourth electrode is placed on the right shoulder in a plane with the other two electrodes on the right. Figure 1B shows the modified Duchosal-Sulzer placement on a patient who is lying down. The Kimura placement has three electrodes on the left side and one on the right, these

From the Department of Cardiology, Hospital for Thoracic and Cardiac Surgery, City of Hope Medical Center, Duarte, California.

being placed at the right midclavicular line in the second right intercostal space, in the second left intercostal space midway between the midclavicular line and the anterior axillary line, and in the back at the same level, being placed opposite the left electrode. The fourth electrode is at the left

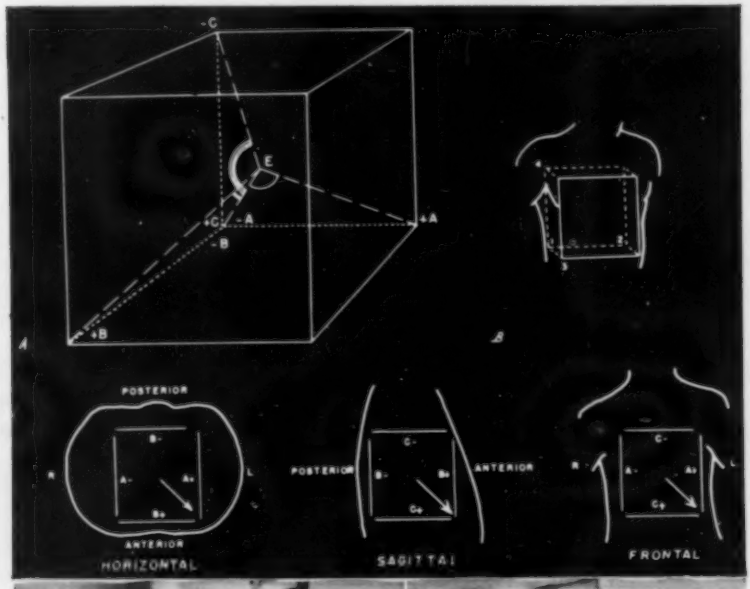

FIG. 1A

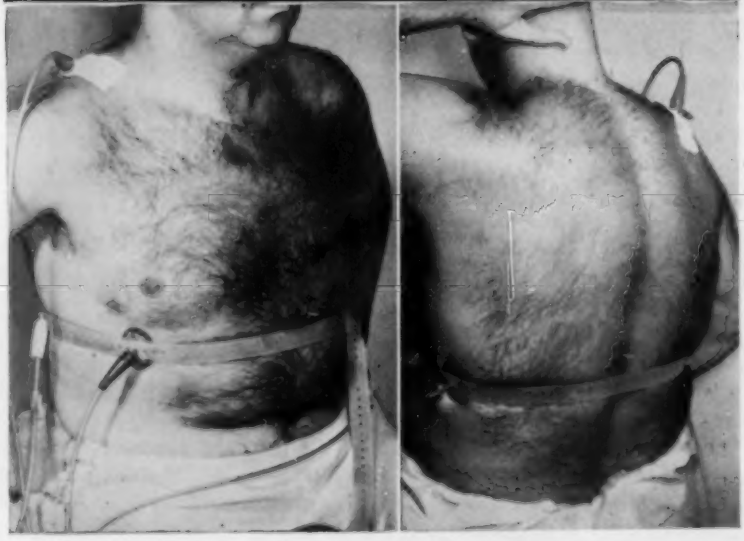

FIG. 1B

Figure 1A: Diagram of cube electrode placement. (Courtesy of Grishman, A. and Scherlis, L.).—*Figure 1B:* Electrode placement on patient, using modified Duchosal-Sulzer placement.

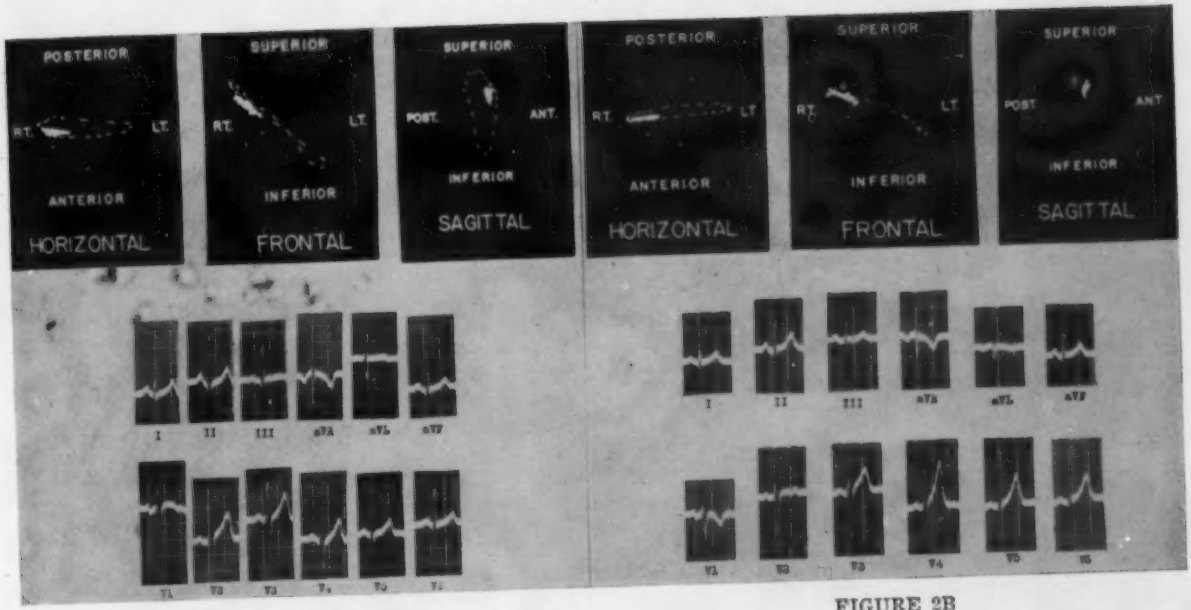

FIGURE 2A

FIGURE 2B

Figure 2A: Vectorcardiogram of normal young adult. Patient's electrocardiogram below.—*Figure 2B:* Vectorcardiogram of normal elderly adult. Patient's electrocardiogram below.

anterior axillary line at the level of the vertebral body L-1. The vectorcardiogram may be recorded utilizing one oscillograph with a switch mechanism so that each plane can be viewed with push-button rapidity, or utilizing three oscillographs so that all three planes, i.e., horizontal or transverse, frontal, and sagittal, may be viewed simultaneously. The trace is interrupted by frequency modulation, permitting time analysis and directional visualization. The segments may be arrow-shaped, pointing in the direction of the rotation of the vector loops. Each segment and each space between segments represents the time interval of interruption. The timing is adjustable. In most instances it is convenient to use 1/400 second; however, other intervals may be utilized for specific studies, especially in studying T and P loops. The nomenclature is derived from electrocardiography. Auricular potential is referred to as P_{AXIS}, ventricular depolarization is QRS_{AXIS}, and ventricular repolarization is T_{AXIS}.

Results

A. Normal. In the young adult with no clinical evidence of heart disease the initial QRS_{AXIS} points to the right, anteriorly and inferiorly or slightly superiorly (Fig. 2A). It then proceeds to the left, inferiorly and posteriorly, and returns to the E point. The initial and terminal phases progress more slowly (segments smaller and closer) than the midportion of the QRS loop. The normal P_{AXIS} loops are usually too small to be clearly identified. The T_{AXIS} loop is well seen but is much smaller than the QRS_{AXIS} loop, and it rotates in the same direction. Although the direction of rotation and contour of the T_{AXIS} loop can be clearly seen in most cases, in recording the loop on film it frequently appears blurred at lower amplifications. It should be noted that the horizontal QRS_{AXIS} loop proceeds in a *counterclockwise* manner and that the sagittal loop proceeds in a clockwise manner. The frontal loop, however, may be either clockwise or counterclockwise and frequently forms a figure of 8.[3, 4] An important point to observe is that the spatial position of the QRS_{AXIS} is in the left inferior octant, a small portion being located in the anterior octant and the larger portion in the posterior octant.

The vectorcardiogram in an elderly adult with a normal heart is shown in Figure 2B. The QRS_{AXIS} is located in the left inferior octant, with only a very small portion of the loop in the anterior octant. However, the routine electrocardiogram of this patient is similar to that of the younger patient previously discussed (Fig. 3).

B. Left Ventricular Hypertrophy. Left ventricular hypertrophy is demonstrated in the vectorcardiogram of Figure 3A. The location of the QRS_{AXIS} is primarily in the left, superior, posterior octant, and the initial portion of the QRS loop arises anterior to the terminal portion. In the horizontal plane, the T_{AXIS} frequently rotates in the opposite direction to the QRS_{AXIS} and is frequently open (Fig. 3B).

C. Left Bundle Branch Block. In the left bundle branch block the QRS_{AXIS} is located primarily in the left superior, posterior octant (Fig. 3C). However, the spacing of the segments of the loop is uneven, showing obvious areas of slower conduction. These areas are scattered and may appear in

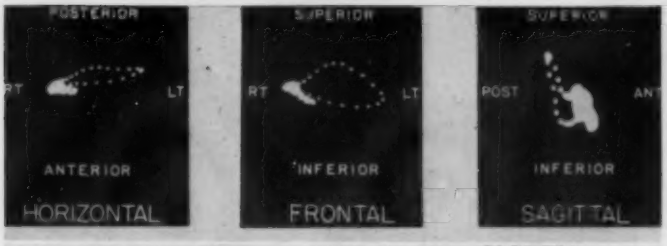

FIG. 3A

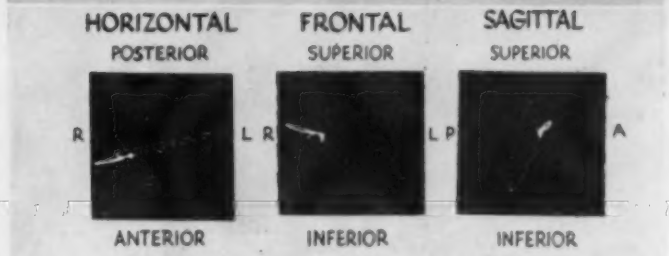

FIG. 3B

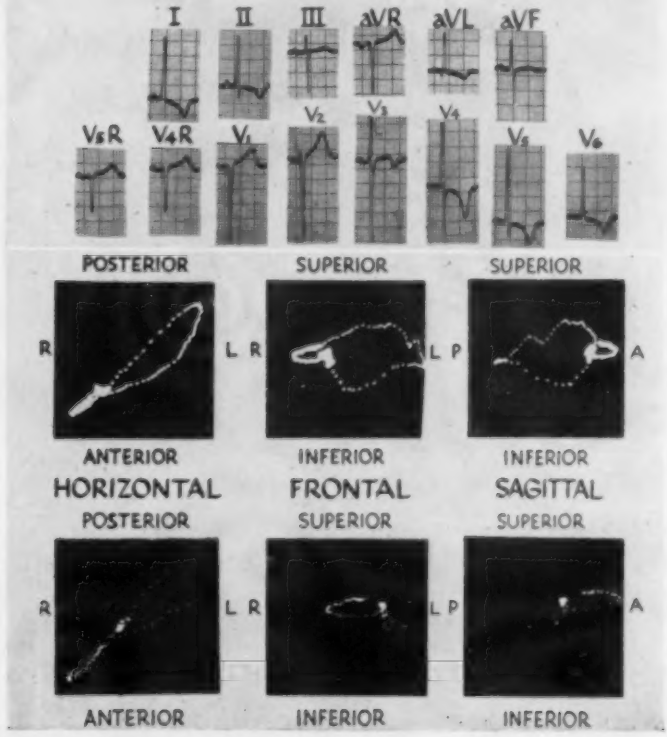

FIG. 3C

Figure 3A: Left ventricular hypertrophy.—*Figure 3B:* Left ventricular hypertrophy. Note open T loops. Patient's electrocardiogram below.—*Figure 3C:* Left bundle branch block. The lower photographs are amplified to allow detailed study of the T loops. The P loops are well visualized also, posterior, inferior, and to the left of the T loop.

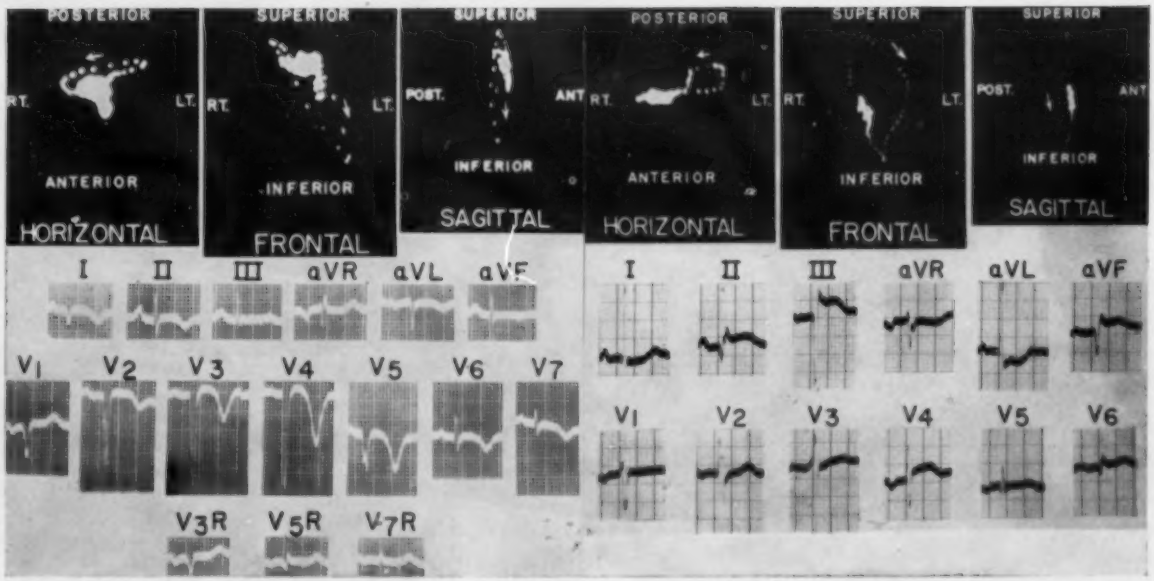

FIGURE 4A

FIGURE 4B

Figure 4A: Anterior myocardial infarction—electrocardiogram below.—*Figure 4B:* Posterior myocardial infarction—electrocardiogram below.

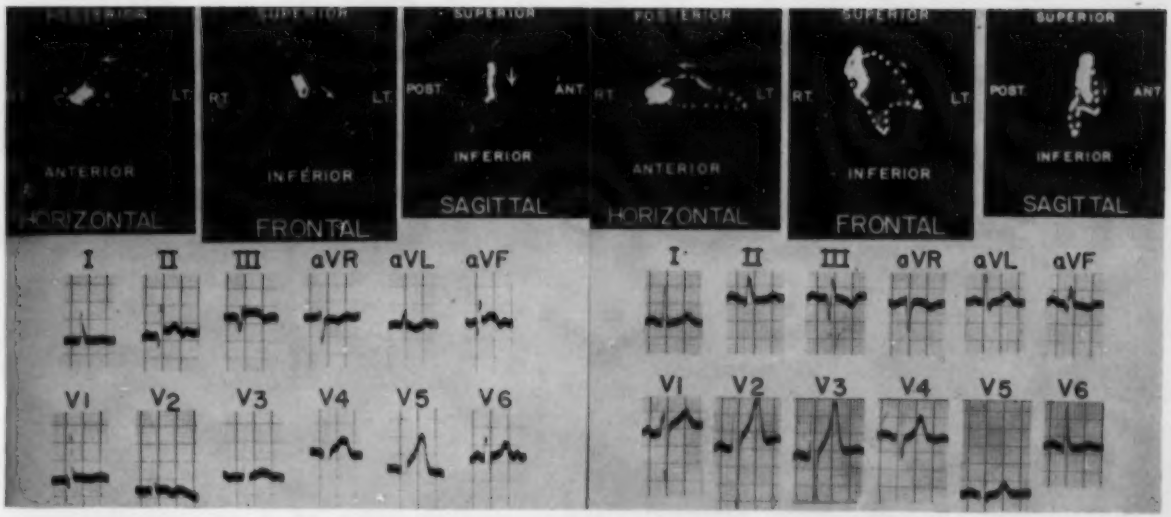

FIGURE 4C

FIGURE 4D

Figure 4C: Lateral wall myocardial infarction—electrocardiogram below.—*Figure 4D:* Myocardial infarction of diaphragmatic (inferior) surface—electrocardiogram below.

the initial portion of the loop, in the mid-portion of the loop, and/or in the terminal portion of the loop. The initial portion of the QRS-a arises posteriorly and the rotation of the loop in the horizontal plane is clockwise, thus demonstrating an obvious differential between left bundle branch block and left ventricular hypertrophy (Fig. 4) in which the initial portion of the loop originates *anteriorly* and the rotation in the horizontal plane is counter-clockwise, unless it is a figure of 8, in which instances the proximal portion of the loop is counter-clockwise.[5] It should be noted that in left bundle branch block repolarization is also abnormal, and open T loop appearing (Fig. 3C).

D. Myocardial Infarction. The vectorcardiogram can be clinically useful in the location of myocardial infarction, because the conduction of electrical impulse is a property of living cells. Therefore, an area of dead muscle would be an area in which electrical potential cannot be demonstrated. This causes a change in the instantaneous vectors at the moment that the area normally would have shown activity. It is manifested by changes in the initial inscription of the vectors and/or by a "shunning" of the involved area. In anterior myocardial infarction (Fig. 4A) the anterior portion of the loop is shunned and the initial QRS-a is directed posteriorly, as is well demonstrated in the horizontal and sagittal planes. Similarly, the QRS-a in posterior myocardial infarction (Fig. 4B) circumvents the involved area, and in myocardial infarction involving the lateral wall (Fig. 4C) the vectorcardiogram demonstrates the lesion by the marked change in contour in that area, giving the impression of circumventing the infarcted area. However, it has been noted frequently, at the autopsy table and at cardiac surgery that, although the electro-

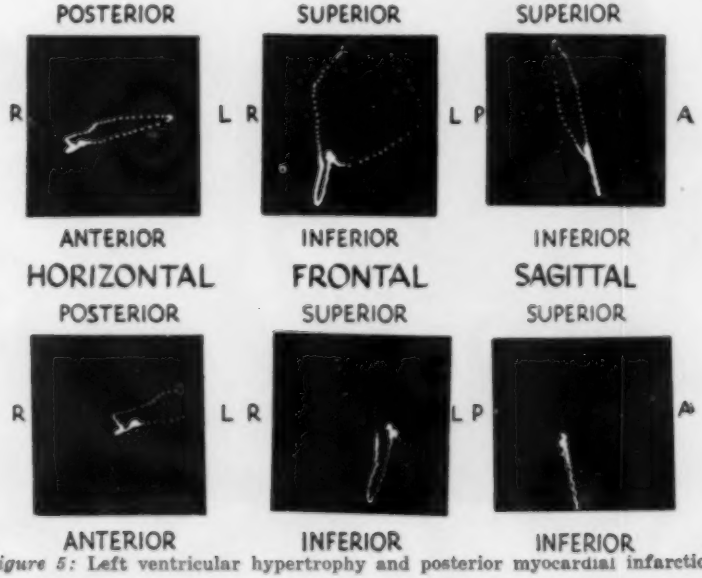

Figure 5: Left ventricular hypertrophy and posterior myocardial infarction.

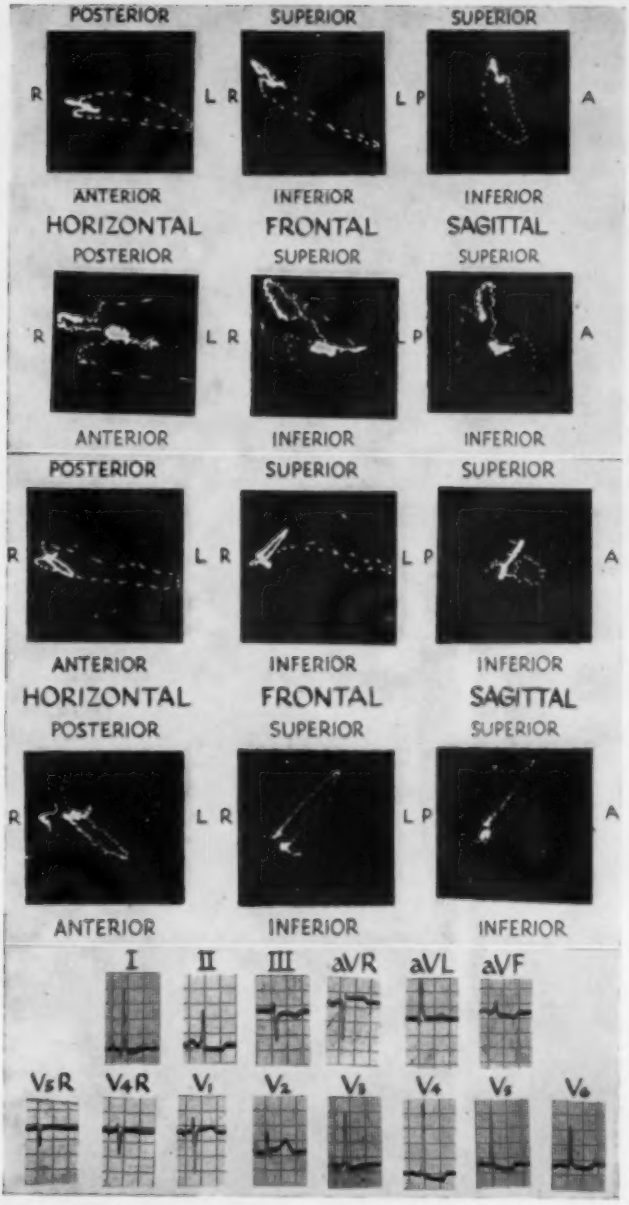

FIG. 6A

FIG. 6B

Figure 6A: Angina pectoris—patient having pain.—*Figure 6B:* Angina pectoris—after nitroglycerin, patient free of pain. The electrocardiogram was taken after patient had nitroglycerin.

cardiogram indicates a posterior infarction, the actual location is the diaphragmatic or inferior surface of the heart. Figure 4D demonstrates an inferior myocardial infarction in a patient in whom the electrocardiogram is interpreted as demonstrating a posterior myocardial infarction.

Direct spatial vectorcardiography can demonstrate an area of infarction in the presence of left ventricular hypertrophy. Figure 5 is the vectorcardiogram of a patient with a history of hypertension and a history of coronary occlusion. The vector is displaced superiorly and posteriorly and the T loops are open and demonstrate abnormal repolarization. The horizontal plane clearly shows the circumvented area of posterior infarction as well.

Another use of the vectorcardiogram clinically may be introduced at this point of our discussion. Figures 6A and 6B are vectorcardiograms of a patient complaining of chest pain. While the first vectorcardiograms were being taken the patient complained of his chest pains. He was given nitroglycerin and the change that resulted is well demonstrated.

E. Right Ventricular Hypertrophy. Direct spatial vectorcardiography has well demonstrated its usefulness in the determination of right ventricular hypertrophy. A recent study[6] (Fig. 7) demonstrates the close correlation between the vectorcardiogram of right ventricular hypertrophy and right ventricular work as measured at cardiac catheterization. Note that, of 25 patients with right ventricular work, the vectorcardiograms showed a right ventricular hypertrophy in 23, whereas the electrocardiogram of right ventricular hypertrophy occurred in 13. In

SUMMARY OF ELECTROCARDIOGRAPHIC AND VECTORCARDIOGRAPHIC DATA IN THE TWO LESIONS AND DIVIDED INTO NORMAL AND ABNORMAL RIGHT VENTRICULAR WORK.

	RIGHT VENTRICULAR WORK UNITS*			
	Greater than 1.06		Less than 1.06	
Total number of patients	25		9	
Mitral Stenosis	9		7	
Congenital Heart Disease	16		2	
	Mitral Stenosis	Congenital Heart Disease	Mitral Stenosis	Congenital Heart Disease
Normal vectorcardiogram	1	1	7	1
Vectorcardiogram of right ventricular hypertrophy	8	15	0	1
Normal electrocardiogram	2	1	7	2
Electrocardiogram of right ventricular hypertrophy	3	10	0	0
Electrocardiogram of incomplete right bundle branch block	4	5	0	0

*Units = kg. M. per minute per sq. M.

FIGURE 7: Chart for comparison of vectorcardiogram and electrocardiogram with right ventricular work (reprint from American Heart Journal, March 1954, p. 377).

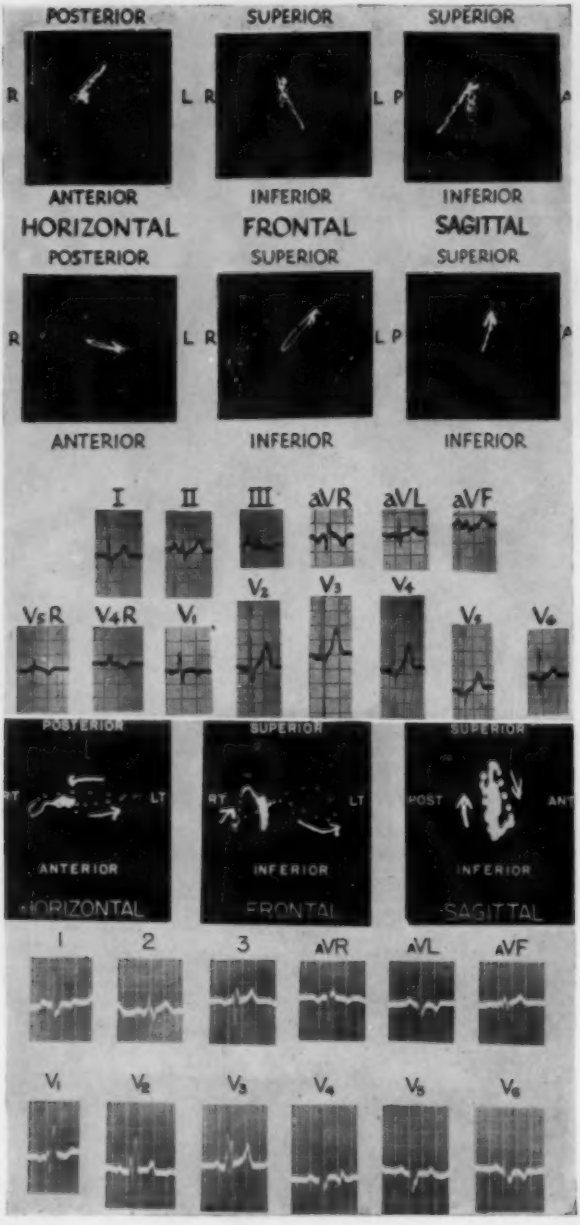

FIG. 8A

FIG. 8B

Figure 8A: Right ventricular hypertrophy—upper vectorcardiogram is with modified Duchosal-Sulzer placement, lower vectorcardiogram is with Kimura placement.—*Figure 8B:* Right bundle branch block.

right ventricular hypertrophy (Fig. 8A) the spatial position of the vector is primarily in the inferior, anterior octant, either partially or totally to the right, the degree depending upon the degree of hypertrophy. Very marked hypertrophy may also cause a posterior displacement of the vector. It should be noted that the rotation of the loop in the horizontal plane is clockwise, as contrasted with the counter-clockwise rotation observed in the normal vectorcardiogram. The lower set of vectorcardiograms in Figure 8A were observed with the Kimura placement.

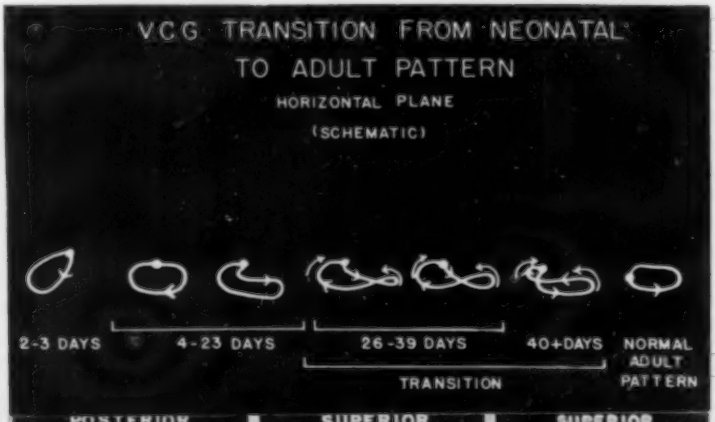

FIG. 9

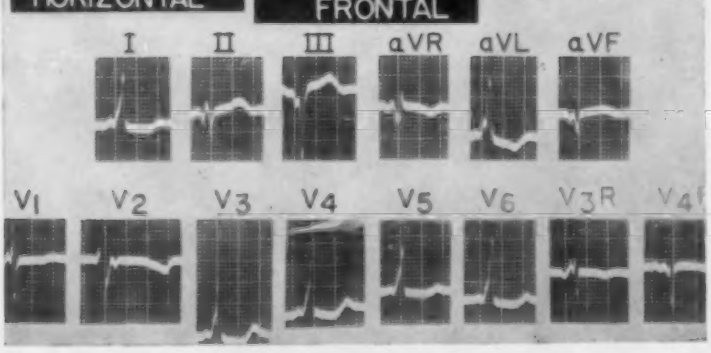

FIG. 10

Figure 9: Diagrammatic representation of transition from "physiological" right ventricular hypertrophy to "normal" vectorcardiogram in infants.—*Figure 10:* Vectorcardiograms of infants 2-4 days of age.

F. Right Bundle Branch Block. When there is a delay in conduction of the right bundle, the vectorcardiogram (Fig. 8B) demonstrates an area of slow conduction in the terminal portion of the QRS$_{x,z}$. The loop rotates counter-clockwise in the horizontal plane. When clockwise rotation is found we probably have both right ventricular hypertrophy and right bundle branch block.

G. Infants. The usefulness of the vectorcardiogram is extended to infants. The transition that has been noted from the neonatal cardiogram to the adult pattern can be demonstrated diagrammatically (Fig. 9).[7] There is an initial, "physiological," right ventricular preponderance at birth. A transition zone occurs some time between the 26th and 40th day of life. It thus becomes feasible to differentiate between "physiological" right ventricular preponderance and "pathological."

H. Unusual Conduction. The vectorcardiogram demonstrates unusual electrical patterns such as those observed in Wolf-Parkinson-White syndrome (Fig. 10). The conduction rate is uneven and the T$_{x,z}$ is open, demonstrating abnormal repolarization.

I. Arrhythmia. Auricular fibrillation can be seen by an obvious irregularity of the heart rate but it cannot be separated from a varying block in auricular flutter. Extrasystoles are clearly seen and are easily differentiated. Ventricular extrasystoles occur at regular or irregular intervals and consist of a bizarre QRS$_{x,z}$ loop which is in the opposite direction to the regular QRS$_{x,z}$ loop. The auricular extrasystoles are similar to, and often identical with, the regular QRS$_{x,z}$.

Acknowledgments: I am grateful to Dr. Alfred Goldman and Dr. George C. Griffith for their guidance and encouragement and to Dr. Alfred W. Kornbluth who has been and is collaborating with me in the study of direct spatial vectorcardiography. I wish to thank Mr. Dick Ray for his assistance in preparing the photographs. Deep gratitude is expressed to Dr. Noboru Kimura for his generous gift of a 3-Scope Vectorcardiograph to the City of Hope Medical Center and for his personal instruction and guidance in the use of this instrument of his own design.

SUMMARY

1. Direct spatial vectorcardiography permits three-dimensional visualization of the electrical activity of the heart and is as simple to employ as a camera-type electrocardiograph.

2. By the use of vectorcardiography we can (a) accurately localize areas of infarction, (b) more accurately delineate left ventricular hypertrophy from left bundle branch block, (c) more accurately determine the presence of right ventricular hypertrophy in infants and adults, (d) identify conduction abnormalities.

3. Direct spatial vectorcardiography is at present inadequate in determining arrhythmias and in evaluating auricular potentials.

RESUMEN

1. La vectorcardiografía directa espacial permite una visualización tridimensional de la actividad eléctrica del corazón y es tan sencilla de emplear como un electrocardiógrafo de tipo cámara.

2. Por el uso de la vectorcardiografía podemos: (a) localizar con ex-

actitud áreas de infarto, (b) Delinear más precisamente la hipertrofia ventricular del bloqueo del haz izquierdo de la rama, (c) determinar más precisamente la presencia de hipertrofia ventricular derecha en niños y en adultos (d) Identificar las anormalida des de conducción.

3. La vectorcardiografía espacial directa es actualmente inadecuada para determinar arritmias y para valuar los potenciales auriculares.

RESUME

1. La vectocardiographie spatiale directe permet la vision en trois dimensions de l'activité électrique du coeur et est aussi simple à utiliser qu'un électrocardiographe classique.

2. Par l'emploi de la vectocardiographie, on peut a) déterminer d'une façon précise la localisation de l'atteinte; b) distinguer plus nettement l'hypertrophie ventriculaire gauche du bloc de branches gauche; c) déterminer plus exactement la présence d'une hypertrophie ventriculaire droite chez les enfants et les adultes; d) identifier les anomalies de conduction.

3. La vectocardiographie spatiale directe est en ce moment incapable d'individualiser les arythmies et d'évaluer les potentiels auriculaires.

ZUSAMMENFASSUNG

1. Die direkte Vector-Cardiographie erlaubt eine dreidimensionale Darstellung der elektrischen Aktivität des Herzens und lässt sich ebenso einfach anwenden wie ein kameraartiger Elektrocardiograph.

2. Durch die Verwendung der Vector-Cardiographie können wir a) Bezirke mit Infarktibildung sorgfältig lokalisieren, b) genauer eine Hypertrophie des linken Ventrikels abgrenzen von einem Block des linken Astes des His'schen Bündels, c) genauer das Vorliegen einer Hypertrophie des rechten Ventrikels bei Kindern und Erwachsenen bestimmen, d) Abweichungen der Überleitung erkennen.

3. Die direkte Vector-Cardiographie ist zur Zeit ungeeignet zur Bestimmung von Arrhythmien und zur Auswertung von Vorhofspotentialen.

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Pancreatic Dornase Aerosol in Pulmonary, Endotracheal and Endobronchial Disease

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Pulmonary complications such as atelectasis, pneumonitis, lung abscess and thick tenaceous sputum are frequently an important factor in morbidity and mortality of many medical diseases and with post-operative and post-traumatic states. Antibiotics have controlled many of the infectious phases of this problem, but the obstructive phenomena remain unsolved. The use of expectorants or vapor inhalations has been of limited usefulness. Endotracheal aspirations or bronchoscopy are frequently necessary, but are traumatic and not always successful even when repeated.

In recent years the use of enzymes and/or enzyme activators such as streptokinase-streptodornase (Varidase), trypsin and of detergents such as alevaire has been popularized. Trypsin has been shown to be effective by many investigators[1-8] but not universally.[9] Serious complications have been reported,[1, 3, 5, 7, 8] and almost all authors advise use of antihistamines[9] and/or epinephrine or ephedrine inhalations with trypsin.[4, 5, 8] The effects of these drugs themselves have not been considered in these reports.

Varidase has been used with less success.[11-14]

Detergents, particularly alevaire, are in common use and have been reported to be effective.[15] Continuous therapy by tent or nasal catheters, or repeated treatments each day for several days are necessary to obtain results.[15]

Pancreatic desoxyribose-nuclease (dornase) prepared by the method of McCarty[16] was first used in patients with thick purulent sputum, such as those with bronchiectasis, with excellent results.[17] Satisfactory results with a purified pancreatic dornase have been reported, with a review of pharmacological effects of the drug.[18] No irritating effects were noted.

Pancreatic dornase and trypsin have been used together with good effect but many serious reactions.[19]

We set out to evaluate the usefulness of this purified pancreatic dornase in all pulmonary conditions presented as unresolved by standard procedures. The local effects and general reactions to dornase were also studied by clinical and laboratory means, including bronchoscopy and pathological examination of resected specimens. The effect of pancreatic dornase on the discovery of malignant disease by cellular cytology from bronchial washings was also studied.

Materials

Pancreatic desoxyribose-nuclease (dornase) was furnished in sterile vials of 100,000 units.* Sterile diluent was supplied in vials of 10 cc.

From the Department of Surgery, New York Hospital and the Department of Thoracic Surgery, Memorial Center for Cancer and Allied Diseases.

*Supplied by Sharp & Dohme Inc., West Point, Pa. Through courtesy of Dr. R. T. Smith

This material is completely soluble in 2 cc. of the diluent. In solution the material loses activity rapidly and should be discarded if not used within an hour. The pH of the material will vary with the amount of diluent used from pH 7.6 with 10 cc. to pH 3.2 with 2 cc.

Methods

In the early cases the 100,000 units of dornase were dissolved in 5 cc. of diluent and 2-3 cc. were used in an aerosol inhalor using oxygen for nebulization at a flow rate of about 5-6 L/minute. The usual rate of use was about 1 cc. in 10-15 minutes. In a few instances hand bulb nebulizers were used but with much less satisfactory results. Since there were no complications or irritation with the first few cases, the concentration was increased to 100,000 units to 2 cc. of diluent in the usual case. In an occasional case where prolonged use was contemplated, the patient was started with the more dilute and later changed to the more concentrated solution. All prebronchoscopy patients except the first 10 were given the more concentrated solution.

Clinical Material

One hundred and four patients, 91 in Memorial Center for Cancer and Allied Diseases, nine in the New York Hospital, and four from other hospitals in New York City, were given dornase inhalations. Results were evaluated by their own physicians, by the author, and by a review of the charts.

With 65 patients pancreatic dornase was used as an aerosol immediately before local anesthetization for bronchoscopy.

Thirty-nine with unresolved pulmonary disease, primary or secondary, were considered therapeutic cases. All had failed to respond to the usual

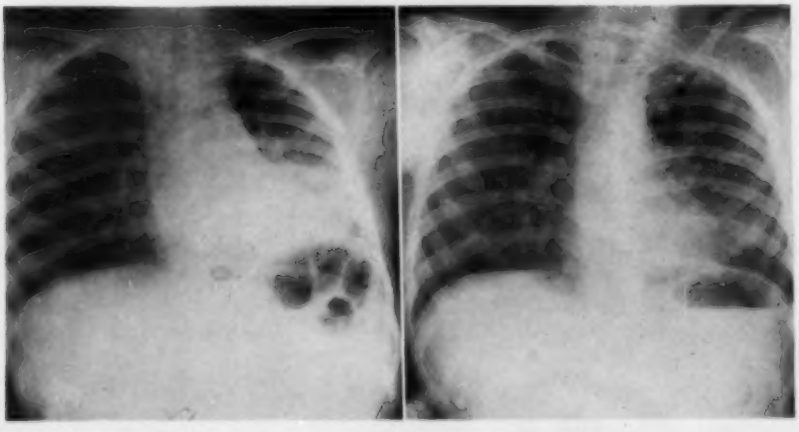

FIGURE 1 FIGURE 2

Figure 1 (Case 1): From x-ray film of December 23, 1954 showing atelectasis of left lower lobe after bronchoscopy and alevaire inhalations.—*Figure 2 (Case 1):* From x-ray film of December 31, 1954 after dornase inhalations showing complete re-expansion of previously atelectatic lobe.

methods of treatment or were actually going down hill while under the usual methods of treatment. Since most of them were seriously ill, it was impossible to discontinue all other treatments at the time of starting dornase. However, in only two instances were definitive drug changes, which themselves could have produced marked improvement, made at the time of or sufficiently close to the time of institution of dornase therapy, to confuse the picture.

Results

1. Prebronchoscopy Cases

Of the 65 patients who received dornase inhalations in preparation for bronchoscopy, 56 bronchoscopies were completed. Twenty-eight of the 56 were ultimately proved to have carcinoma of the lung. Of these, 20 (71 per cent) had positive or suspicious cytological studies on this single examination. In contrast the washings of 26 patients without carcinoma were reported negative by our cytologists.

There were no complications or reactions to the dornase in this group of 65 cases. The mucosa appeared normal throughout except where disease was present and biopsies of the mucosa in instances negative for tumor failed to show any reaction. One with chronic bronchitis gave the typical picture for that disease. Two patients had active tuberculosis proved by smears and culture, and there was no subsequent evidence of spread or increase in the disease process. Three others had inactive tuberculosis or Boecks Sarcoid with no evidence of increase in the disease. Two coughed up large bronchial plugs following the inhalation before actual passage of the bronchoscope with definite relief of symptoms of chronic cough and segmental atelectasis.

2. Therapeutic Cases

Thirty-nine patients with uncontrolled pulmonary complications or disease were treated with dornase. Of these, 13 were cured of the pulmonary complication or disease, 12 were markedly and permanently improved and eight were improved temporarily, while receiving dornase and for limited periods after its use. Only three were unchanged, and in three it was impossible to evaluate the results satisfactorily.

There was no serious complication from the use of dornase and only four patients had symptoms which could possibly have been due to the enzyme. Two complained of nausea after the inhalations; one was receiving radiation therapy for carcinoma of the lung and had been nauseated before the dornase was started, the other postoperative atelectasis following gastrectomy and suffered from dumping syndrome. Two patients had sore throats, both during a second course of therapy. In only one of them does dornase seem to be implicated justifiably with irritation after each inhalation in the second course of treatment. The second patient had a severe monilia infection secondary to heavy antibiotic dosage.

The best and most dramatic results were with those having atelectasis, all being cured by relatively few (3 to 5) treatments. The next best results

were in those with thick tenaceous mucus with partial segmental atelectasis and great difficulty raising the sputum, making naso-tracheal aspirations necessary in many cases, before dornase was used. The poorest results were in those with pulmonary complications secondary to advanced malignant intrathoracic tumors.

Group I—Patients with Atelectasis—Four patients with lobar atelectasis; two with undetermined origin, and two post-operatively showed complete relief of symptoms and objective physical signs or x-ray film evidence of complete relief of the atelectasis.

Case No. 1, F. W., Norwegian Hospital. This eight year old boy had a proved atelectasis of the left lower lobe, by symptoms, physical findings and x-ray films. He had received alevaire inhalations and had been bronchoscoped on two occasions in an attempt to relieve the atelectasis. The condition only became worse (Fig. 1). He received two inhalations of pancreatic dornase on December 29, and one on December 30, 1954. Following this, there was complete relief of the atelectasis by symptoms, physical signs and x-ray film (Fig. 2). He was entirely well until May 1955, when he had a second attack of atelectasis, again relieved completely by two inhalations of pancreatic dornase.

Case No. 2, R. B., Memorial Hospital No. 40688, was a 49 year old white female with clinical and x-ray evidence of right middle lobe and right lower lobe atelectasis. She had been treated in another hospital for two weeks with aerosols, antibiotics and bronchoscopy without relief and was admitted to Memorial Hospital on January 9, 1955, for resection of a probable tumor. She received five inhalations of pancreatic dornase from January 11 to 14, 1955, with increase in sputum after each of the first four, and

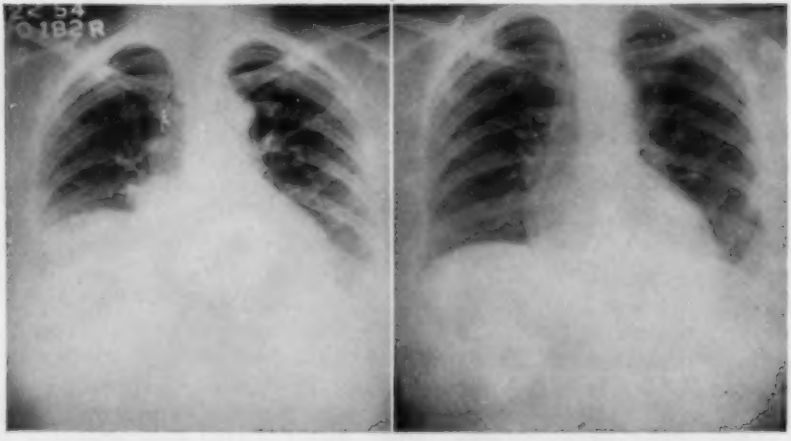

FIGURE 3 FIGURE 4

Figure 3 (Case 3): From x-ray film of December 22, 1954 showing evidence of right lower and right middle lobe atelectasis with elevation of diaphragm.—*Figure 4 (Case 4):* From x-ray film of January 10, 1955 identical with that of January 6, 1955 which reproduced poorly, showing complete relief of atelectasis.

expectoration of a large bronchial plug 3 to 4 cm. long and about ¼ cm. in diameter, after the fifth inhalation. This gave complete relief of symptoms and she was discharged two days later as cured with normal chest x-ray film.

Case No. 3, M. D., Memorial Hospital No. 38976. This 52 year old white woman had radical cystectomy performed on December 14, 1954. By December 17, she was known to have atelectasis of the right lower lobe with elevation of the diaphragm and displacement of the mediastinum to the right. She was treated with naso-tracheal aspirations daily, obtaining some secretion, but no improvement of the atelectasis was shown by clinical signs or by x-ray films on December 20, 22, and 27 (Fig. 3). On December 28, after fluoroscopy which showed no change she was started on pancreatic dornase twice daily (100,000 units/5 cc.). The following day, there was improvement of the atelectasis by physical examination and fluoroscopy. On December 31, she was discharged after complete clearing of the chest was demonstrated on physical examination and by fluoroscopy, confirmed by x-ray films of the chest (Fig. 4).

Case 4 was similar in diagnosis, treatment and results.

Group II—Patients with Pulmonary Complications of Medical Diseases—Four patients with thick mucoid secretions and segmental atelectasis associated with serious chronic diseases, were treated with dornase.

They were acutely and chronically ill with serious primary diseases, with superimposed pulmonary complication. All had been treated actively for both the primary disease and the pulmonary complications without significant improvement before being considered for dornase therapy. This included continuous alevaire by tent or frequent alevaire inhalations. All responded well to dornase. Cases No. 5, 6 and 7 could be considered as completely cured of their pulmonary complication. With case No. 5 with hypertensive cardiovascular disease and pulmonary edema, and Case No. 6, with lupus erythematosus, all other drugs for treatment of the pulmonary complication were discontinued at the beginning of dornase. Both had complete relief of the pulmonary complication after two and three days of treatment.

Case No. 7, W. T., New York Hospital No. 696633. This 70 year old white man was admitted to New York Hospital on March 18, 1955, with severe cerebral vascular accident, hypertensive cardiovascular disease and pulmonary edema. He was placed on apresoline, hexamethonium, penicillin and streptomycin and other drugs for relief of pulmonary edema and control of symptoms. He was unable to raise the thick tenaceous bronchial secretions. Frequent endotracheal aspirations were necessary and he was on alevaire inhalations from March 26, with only increasing difficulty from his pulmonary disease. Increased congestion and patches of pneumonitis were observed on the x-ray film on March 24. There was steady progression of symptoms until March 27, when he was cyanotic while out of the tent and had obvious left lower lobe consolidation with temperature of 39.0° C. This day he went into shock and looked moribund according to his attending physician's note. Levophed was started and

naso-tracheal aspirations were necessary at least every 20 minutes. Despite this, the lungs could not be kept clear. On March 28, his temperature was 40.0° C., he was still in shock and was cyanotic even in oxygen. Following the first inhalation of pancreatic dornase, it was noted that it was easier to aspirate the sputum and his lungs cleared more than previously. He was given two inhalations that day and then was started on tetracyclene 250 milligrams every eight hours. On March 28, he was much improved but still slightly cyanotic when out of the tent for a short time. His temperature was 38.6° C. By March 30, he was able to aspirate himself and to sit up and feed himself. His lungs were almost clear, the sputum was much less viscid and he was able to cough it up most of the time and only had to be aspirated or aspirate himself infrequently. His temperature was 37.7° C. Dornase was discontinued April 2. His course continued to show improvement and he was discharged about one month later.

Case No. 8 was only temporarily improved after each treatment and for a short time after each of the two courses of treatment. With the first course other treatments were continued but for the second all other treatments were discontinued, with no change in results.

Group III—Post Thoracotomy Patients—Eight patients who had thoracotomy with rib resection were treated for thick tenaceous sputum, and/or segmental atelectasis or pneumonitis. This type of patient is particularly difficult to manage because of the already poor pulmonary function and poor tolerance to further loss of function and their inability in many instances to develop effective cough because of chest pain and the poor respiratory exchange. Naso-tracheal aspirations are frequently effective, but are time-consuming, unpleasant to the patient and complications may follow their frequent use. Bronchoscopy is limited in frequency.

In these eight patients, naso-tracheal aspirations were unnecessary after the start of dornase inhalations. Four of them were considered cured of their pulmonary complications by relatively few inhalations, two in two cases, three in one and six in the fourth. These results were almost as dramatic as were those in the patients with lobar atelectasis.

Case No. 12, J. S., Memorial Hospital No. 42306 is an example of the four cured cases. This 72 year old white male had upper lobectomy March 15, 1953, for metastatic carcinoma of the lung, when tracheostomy was performed because of expected respiratory difficulty. Post-operatively he had difficulty with thick mucoid sputum, necessitating frequent aspiration through the tracheostomy and still with failure to clear the lungs of numerous coarse, moist rales. On the fourth post-operative day, he developed fever of 103° F. due to focal atelectasis confirmed by x-ray. Two inhalations of dornase (100,000 units/2 cc.) were given on March 22 and 23. Following the first treatment, the secretions thinned and the patient was able to raise them much more easily, and there was no further necessity for endotracheal aspirations. His temperature fell on the next day and he was discharged three days later on the 13th post-operative day.

A fifth patient had marked improvement in fluidity and ease of raising the sputum, but his fever was not markedly changed by the drug and so he

could not be considered cured. He was one of the two who suffered from sore throat and mouth which in his case was shown to be due to severe monilia infection, secondary to massive antibiotic treatment.

Two had only temporary improvement with decrease in viscosity of tenaceous sputum and ease in suctioning sputum. Both succumbed to their disease the day after beginning treatment.

Only one failed to show any definite improvement.

Group IV—Patients with Advanced Intrathoracic Carcinoma—These 10 patients obviously were poor cases for any type of treatment, but the complication of thick tenaceous mucus, or atelectasis was considered so serious as to warrant all possible attempts to relieve them.

Only one could be considered as being completely relieved of complication. Case No. 17, P. I., Memorial Hospital No. 39681. This 65 year old white man had been explored on September 24, 1954, when a non-resectable carcinoma of the left lung with abscess formation was found. He developed complete atelectasis of the lung by the fourth post-operative day and four days later had spiking fever with chills. For the next month he continued to have temperature elevation to 100° to 102° F. in spite of crysticillin, gantrisin, chloromycetin and terramycin in large doses. On the 46th post-operative day he was started on pancreatic dornase by inhalations. There was rapid defervescence of fever, improvement in his appetite, in his general feeling of well being and ease of expectoration with at first an increase in the amount of sputum to a large quantity, and then decrease in sputum. The temperature rose to above 99° F. only two times after November 11. He was discharged on November 22. For three days before discharge, he had been completely free of fever without significant cough or distress in his chest and feeling better than at any time during his hospitalization.

Four other patients were definitely improved, giving a total of five (50 per cent) in this group who showed definite improvement. One of these patients had two courses of dornase with temporary improvement after each.

Four had temporary improvement during the time of actual use of dornase with regression after it was discontinued. One of them, F. S., Memorial Hospital No. 36903 was the second of the two who complained of irritation of the mouth and throat during his second course of treatment. Only one, an outpatient receiving one inhalation daily for dry cough, while receiving radiation therapy to the chest was unimproved.

Group V—Patients with Tracheostomy—Three patients were treated in this group. Two with so-called tracheitis sica, and one with temporary difficulty with tenaceous sputum after total laryngectomy and tracheostomy. The latter received only one treatment with temporary improvement.

The two with tracheitis sica were severe cases with thick sputum and plugs, with frequent obstruction necessitating emergency aspirations as well as frequent cleansing of the tracheostomy. One of over a month's duration was completely relieved after 12 daily instillations as an outpatient. The second had three courses of treatment with complete relief during the treatment, and with recurrence when dornase was discontinued between

the first and second and the second and third courses. Following the last course he was completely relieved. The third had only one inhalation which resulted in improvement of his condition.

Group VI—Miscellaneous—This group comprises seven patients, all different in their basic disease process and pulmonary problem.

Case No. 30, V. K., New York Hospital No. 705707, a 39 year old white male was admitted on March 18, 1956, with cellulitis of the nose and lung abscess evidently of long duration. He had cough with thick tenaceous sputum and temperature of 39.5° C. He was given penicillin 600,000 units every eight hours from March 18 to 24, and 250 mgm. of achromycin every four hours from March 22 to 25. He was on streptomycin from March 24, until April 23. There was no change in the lung abscess with antibiotic therapy (Fig. 5), and he continued to have fever of 38.6° C. to 39.5° C. He was started on pancreatic dornase on March 27, when he received two inhalations. Two were administered on March 28. He was bronchoscoped on March 30, but there was no positive finding. Pancreatic dornase three times daily was reinstituted on April 1, when the temperature rose only to 37.8° C. and thereafter remained essentially normal until April 9, when dornase inhalations were discontinued. At this time he had had temperature of 37.3° C. for three consecutive days and the abscess cavity could not be visualized on routine posterior anterior and lateral x-ray films (Fig. 6). On April 10, after stopping dornase, his temperature was 37.8° C. and it remained persistently 37.8° C. throughout his hospital course until toward the end of hospitalization. Tomograms were taken on April 19, which showed a very small cavity present in the center of the area of the previous abscess cavity. He was continued on bed rest and nothing but streptomycin treatment through May 10, when he was again placed on dornase three

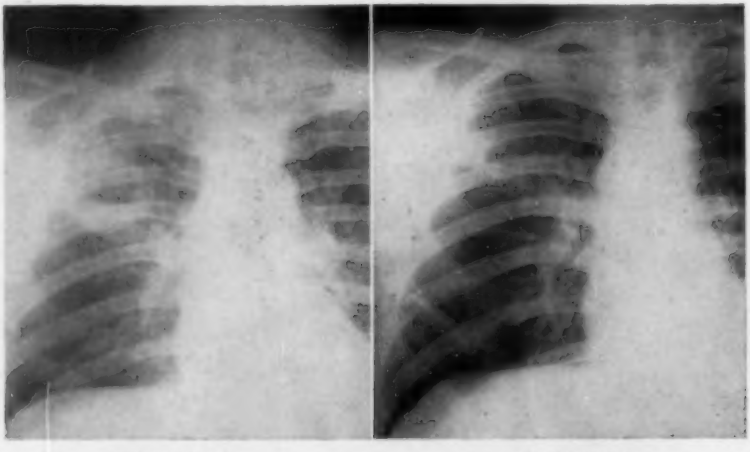

FIGURE 5 FIGURE 6

Figure 5 (Case 30): From x-ray film of March 26, 1955 showing abscess cavity which had increased slightly in size while on antibiotics.—*Figure 6 (Case 30):* From x-ray film of April 8, 1955 after 11 days of dornase, and the day before it was stopped. Note failure to demonstrate cavity, though changes remain in the area.

times a day for three and one-half days. His temperature dropped from 38° C. to 37.5° C. Tomograms on May 14, showed no evidence of cavity and he was discharged.

Case No. 31, H. P., Memorial Hospital No. 38346 was a 57 year old white male ultimately shown at operation to have lipoid pneumonia. With six inhalations of dornase he improved clinically and even by x-ray film. Pathological examination of the resected lobe failed to show any unusual bronchial or alveolar changes due to dornase.

Case No. 32, H. McC., New York Hospital No. 706642. This 65 year old colored window washer had multiple rib fractures and other severe injuries. He was unable to cough up thick tenaceous sputum because of chest pain and was rapidly developing signs of atelectasis and pneumonitis with fever to 101° F. by the day after admission despite antibiotics. Two hours after the first inhalation there was thinning and increased ease in raising the sputum. There was lysis of fever and clearing of pulmonary signs in three days.

Case No. 33, K. B., Memorial Hospital No. 16156. This 47 year old white woman with asthmatic bronchitis and segmental atelectasis had marked improvement with inhalations of dornase at weekly intervals. Prolonged improvement followed the last inhalation after which she coughed up two large (2 cm. x ¼ cm.) and several smaller plugs.

Two other patients also showed definite improvement. The last patient was moribund and though he showed marked thinning of the sputum permitting easier aspiration, succumbed to his general disease.

Group VII—Indeterminate Cases—Three patients could not be properly evaluated because of inadequacy of records. None of them had any undesirable reaction to the drug.

Discussion

From our results and previously reported series of cases, pancreatic dornase would seem to be a useful tool in controlling pulmonary disease secondary to plugging of bronchi by mucoid or thick purulent secretions. Results have been excellent in those patients with acute disease and there has been improvement in almost all cases treated, even those with far advanced disease.

In general it was noted that with the first inhalation of dornase there was loosening of secretions and cough and increase in the quantity of sputum to double or triple that previously obtained. This might continue for three or four treatments and with the few resistant cases it continued even longer. In the satisfactory cases this increase would occur with only the first or second treatment. Following the period of increased secretion there would be rapid decrease in the amout of sputum until in those rated cured or improved there was no significant sputum production. This course of events would lead to the opinion that the dornase effect was not one of irritation but rather an actual lysing of the sputum permitting clearing of the airway.

These good results have been obtained, happily, without serious complications of the treatment itself. Indeed, there have been few reactions of

any type even with prolonged use and with repeated courses of treatment. Two patients had sore mouths following dornase but only one was thought to be properly blamed on dornase, the other probably being due to monilia infection. Two had nausea and vomiting after dornase but both had other reasons: one had a dumping syndrome and the other was receiving radiation therapy. Only one in this entire group asked to have the dornase discontinued. This is in contradistinction to trypsin which, although also effective, has been followed frequently by severe irritation and some serious reactions.

Studies of the bronchial tree by bronchoscopy failed to show any significant change in 56 patients studied. Biopsies and cellular cytology likewise failed to reveal any demonstrable change, which is at variance with the results following trypsin where metaplasia has been reported.

In those in whom complete cure of an acute lesion such as atelectasis is to be obtained, this usually occurs with relatively few inhalations. In more chronic diseases such as tracheitis sica and chronic lung abscess, or lung abscesses secondary to tumor longer courses have been necessary.

Unfortunately we have had only two questionable asthmatics, since these as a group have given unsatisfactory results with inhalation therapy with enzymes alone or alevaire alone in most reported series. Our two cases were both improved. Two others coughed up large bronchial plugs with relief of symptoms, although not proved to be asthmatic patients.

SUMMARY

Pancreatic dornase has been used in a total of 104 patients, in two groups: Group 1: 65 who received inhalations before bronchoscopy, and Group II: 39 who received inhalations for treatment of pulmonary disease.

None of the 65 who had inhalations before bronchoscopy had any reaction to the drug. Sixteen of the 28 proved carcinomas (57 per cent) gave positive cytologies and 20, (71 per cent) gave positive or doubtful cytologies. There were no false positives.

Patients with acute pulmonary disease such as atelectasis secondary to mucus plugs or thick tenaceous sputum respond most rapidly and satisfactorily to pancreatic dornase. Those with more chronic disease respond slower but remarkably well, while those with advanced malignant disease or chronic pulmonary disease with dry cough, such as post-radiation bronchitis, respond less satisfactorily or poorly to the drug.

Even with repeated inhalations and repeated courses of inhalations, only a few had minor complications.

This enzyme would seem to be particularly useful in post-operative thoracic surgical and post-traumatic patients with thoracic injuries.

RESUMEN

Se ha empleado la dornasa pancreática en 104 enfermos correspondientes a dos grupos:

Grupo I: 65 que recibieron inhalaciones antes de broncoscopía y Grupo II: 39 que recibieron inhalaciones para el tratamiento de una enfermedad pulmonar.

Ninguno de los 65 que tuvieron inhalaciones antes de broncoscopía tuvieron reacción alguna a la droga. Dieciseis de los 28 carcinomas demostrados (57 por ciento) dieron citología positiva y 20 (71 por ciento) dieron citologías positivas o dudosas. No hubo falsos positivos.

Los enfermos con enfermedad pulmonar aguda tal como la atelectasia secundaria a tapones mucosos y a esputos espeso tenaz, respondieron más rápidamente y satisfactoriamente a la dornasa pancreática.

Aquéllos con enfermedad más crónica respondieron más lentamente pero notablemente bien en tanto que los que tenían enfermedad maligna o enfermedad crónica con tos seca, tales como los de bronquitis post-irradiación, respondieron menos satisfactoriamente o de modo deficiente a la droga.

Aún con inhalaciones repetidas y series reiteradas de inhalaciones sólo unos pocos tuvieron complicaciones menores.

Esta enzima parece ser especialmente útil en los recien operados de tórax y después de traumatismos con daño torácico.

RESUME

L'auteur a utilisé la "dornase pancréatique" sur un total de 104 malades répartis en deux groupes: le groupe I comporte 65 malades, qui reçurent des inhalations avant bronchoscopie, le groupe II 39 malades, qui reçurent des inhalations pour traiter une affection pulmonaire.

Aucun des 65 malades qui eurent des inhalations avant la bronchoscopie, n'eut la moindre réaction au produit. 16 malades parmi les 28 carcinomes reconnus (57%) donnèrent des cytologies positives, et 20 (71%) des cytologies positives ou douteuses. Il n'y eut aucune réponse positive fausse.

Les malades atteints d'affection pulmonaire aiguë telle que atélectasie secondaire à des bouchons muqueux ou à une expectoration épaisse et tenace, répondirent le plus rapidement et de la façon la plus satisfaisante à la "dornase pancréatique." Ceux atteints d'affections plus chroniques répondirent plus lentement, mais remarquablement bien, tandis que ceux atteints d'une affection maligne, d'une affection pulmonaire chronique, avec toux sèche, telle que bronchite post-radiothérapique, répondent d'une façon moins satisfaisante, ou faiblement au produit.

Même avec des inhalations répétées, et des séries répétées d'inhalations, un petit nombre seulement de malades eurent des complications secondaires.

Cet enzyme semblerait particulièrement utile dans la chirurgie thoracique post-opératoire, et pour les malades atteints de traumatismes thoraciques.

ZUSAMMENFASSUNG

Die Pancreas-Dornase wurde bei insgesamt 104 Kranken in 2 Gruppen gebraucht: Gruppe I: 65, die Inhalationen erhielten vor einer Bronchoskopie, und Gruppe II: 39, die Inhalationen bekamen zur Behandlung pulmonaler Erkrankungen.

Keiner der 65, die vor der Bronchoskopie inhaliert hatten, hatte irgend

eine Reaktion auf das Medikament. 16 der 28 nachgewiesenen Carcinome (57%) ergaben positive cytologische Befunde und 20 (71%) ergaben positive oder zweifelhafte cytologische Befunde. Irrtümlich positive Befunde kamen nicht vor.

Kranke mit akuter pulmonaler Erkrankung so wie Atelektase infolge Schleimpfropf oder dickem, zähem Sputum reagieren besonders schnell und befriedigend auf Pancreas-Dornase. Diejenigen mit mehr chronischen Erkrankungen reagieren langsamer, aber bemerkenswert gut, während diejenigen mit fortgeschrittener bösartiger Erkrankung oder chronischer Lungenkrankheit mit trockenem Husten sowie bei Bronchitis nach Bestrahlung weniger befriedigend oder schlecht auf das Mittel ansprechen.

Selbst bei wiederholten Inhalationen und wiederholten Serien von Inhalationen bekamen nur wenige Kranke leichtere Komplikationen. Dieses Enzym scheint besonders nützlich zu sein in der Nachbehandlung von Thorax-Operationen und bei Kranken nach Trauma mit Thoraxverletzung.

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Further Experiences with the Clinical Use of Streptomycylidene Isonicotinyl Hydrazine Sulfate in the Therapy of Pulmonary Tuberculosis*

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Previous studies have reported on clinical experiences of this service with streptomycylidene isonicotinyl hydrazine sulfate given intermittently in the therapy of pulmonary tuberculosis.[1, 2]

A preliminary report in 1954 indicated that streptomycylidene isonicotinyl hydrazine sulfate given intramuscularly in doses of 1.4 grams twice weekly was comparable to regimens employing daily isoniazid and sodium para-aminosalicylic acid or intermittent streptomycin.[3]

At that time a significant initial advantage in the rate of apparent cavity closure appeared to exist in favor of the previously untreated group on intermittent streptomycylidene isonicotinyl hydrazine sulfate versus the no previous treatment group on daily isoniazid. When all patients were compared, daily isoniazid regimens showed a more favorable proportion of cultural conversions than the entire group on intermittent streptomycylidene isonicotinyl hydrazine sulfate therapy at 16 weeks and 24 weeks. Other differences in clinical effects, conversion of cultures and x-ray improvement, were found not significant.

The present study is an extension of results previously reported. The number and duration of observations is more complete and more reliable statistically. All patients on intermittent therapy here reported had eight months or more of treatment. All others are excluded from statistical analysis.

Description of Patients and Method of Study

Tables I, II and III describe the patient groups reported as to extent of disease, trend toward improvement or worsening at the start of the study, and duration of prior therapy with streptomycin or isoniazid.

Since reliable comparisons are impossible when prior treatment patients are compared to those on an original treatment course for tuberculosis, these are separated for study. Two comparative tabulations will be used. All patients receiving intermittent streptomycylidene isonicotinyl hydrazine sulfate compared to all patients receiving daily isoniazid and sodium

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The Streptomycylidene Isonicotinyl Hydrazine Sulfate used in this study was supplied as "Streptohydrazid" by Dr. Gladys L. Hobby of the Research Laboratories, Chas. Pfizer & Co., Inc., Brooklyn, New York.

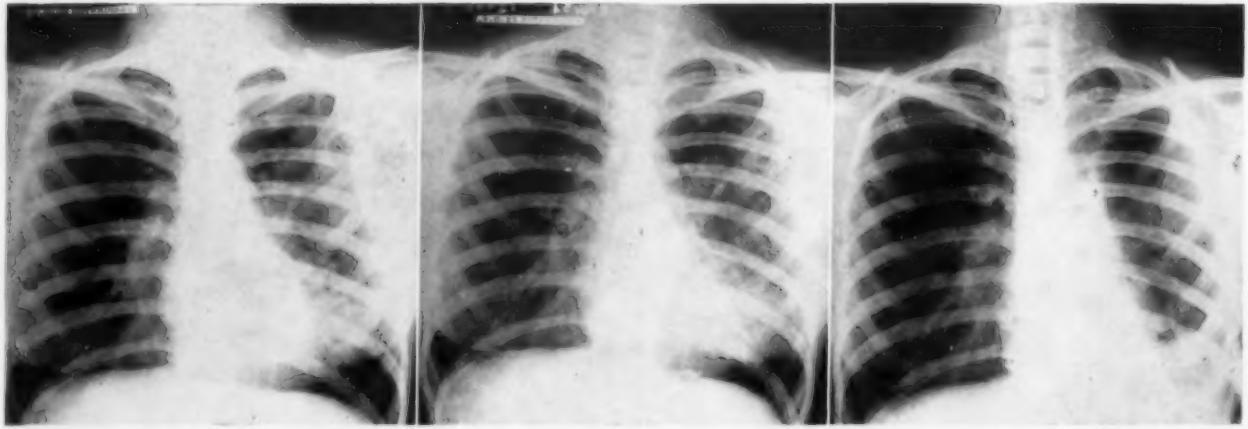

FIGURE 1A FIGURE 1B FIGURE 1C

Figure 1A (PATIENT EW): Initial chest film of September 29, 1954 showing tension cavity in left upper lobe. Patient receiving SIH, 1.4 grams daily for 30 days.—*Figure 1B*: Chest film of November 16, 1954 following change to intermittent SIH, 1.4 grams bi-weekly. Some clearing of infiltration is shown with little change in the size or character of cavity.—*Figure 1C*: Chest film of January 17, 1955 following removal of upper and lingular lobes.

POSITIVE CULTURES FOR
M. TUBERCULOSIS

ORIGINAL TREATMENT
GROUP

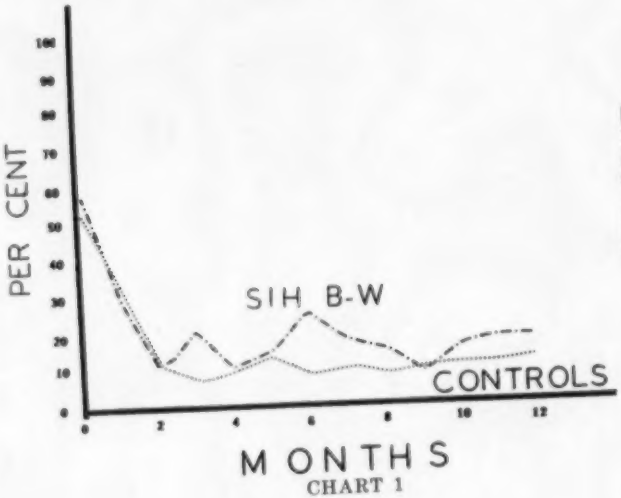

CHART 1

POSITIVE CULTURES FOR
M. TUBERCULOSIS

ALL PATIENTS

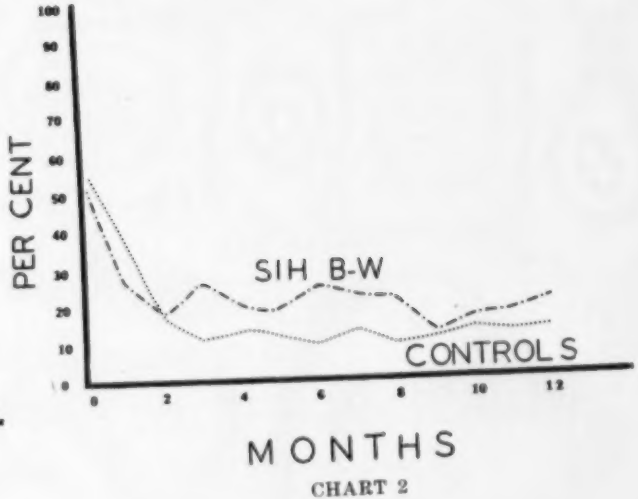

CHART 2

para-aminosalicylic acid or streptomycin twice weekly (controls) and original treatment patients receiving intermittent streptomycylidene isonicotinyl hydrazine sulfate compared to original treatment controls.

TABLE I
DESCRIPTION OF 93 SIH TREATED PATIENTS AND 87 CONTROL PATIENTS BY DISEASE EXTENT**

	INTERMITTENT SIH GROUP		CONTROL GROUP	
	Original	Prior Therapy	Original	Prior Therapy
F.A.	20	29	37	15
M.A.	18	18	22	8
MIN.	4	4	3	2
Sub-Totals	42	51	62	25
TOTALS	93		87	

**SIH refers to Streptomycylidene Isonicotinyl Hydrazine Sulfate.

TABLE II
IMPROVEMENT VS. WORSENING AT START OF THERAPY

	INTERMITTENT SIH GROUP Original	CONTROL GROUP Original	INTERMITTENT SIH GROUP Prior Therapy	CONTROL GROUP Prior Therapy
Improving	13	11	15	7
Non-Progressive	2	12	17	9
Worsening	27	39	19	9
TOTALS	42	62	51	25

TABLE III
DISTRIBUTION OF ALL PATIENTS STUDIED BY DURATION OF PRIOR TREATMENT WITH STREPTOMYCIN AND/OR ISONIAZID

PERIOD	INTERMITTENT SIH GROUP	CONTROL GROUP
0 - ½	42	56
1 - 11	18	15
12+	33	16
TOTALS	93	87

In these tables, it will be noted that a bias exists in favor of the test regimen in that the proportion of far advanced and clinically worsening patients was higher at the start of therapy in the original treatment control group. *This must be kept in mind in the interpretation of clinical and laboratory results.*

The age and sex distribution of patients in the therapeutic test groups was comparable.

Toxicity

Toxic response to the injection of streptomycylidene isonicotinyl hydrazine was observed as an immediate reaction to the first dose in nine of 50 patients who had prior streptomycin for from four to 12 months. Symptoms were hyperaesthesia, tinnitus, vertigo, nausea, itching beginning 15

to 90 minutes after injection of streptomycin. Streptomycylidene isonicotinyl hydrazine sulfate was discontinued in all in the first two weeks.

Original treatment patients who experienced paresthesia, tinnitus and vertigo were two who after 12 months of intramuscular streptomycylidene isonicotinyl hydrazine sulfate bi-weekly, were changed to streptomycin, 1 gram bi-weekly and sodium para-aminosalicylic acid daily.

No other significant toxic responses were discerned.

Drug Failures

Progression of tuberculous disease in the lung and exacerbation of clinical symptoms occurred in one original therapy patient treated with intermittent streptomycylidene isonicotinyl hydrazine sulfate. This patient showed worsening after 11 months although bacilli remained sensitive to both isoniazid and streptomycin.

Nine prior patients on intermittent streptomycylidene isonicotinyl hydrazine sulfate have received from 7½ to 8½ months of prior therapy with streptomycin or isoniazid. These developed roentgenographic evidence of spread and clinical signs of worsening after from 8½ to 9½ months of intermittent therapy. All of these patients had initial evidence of repeated previous cultures showing resistant organisms to either streptomycin, 30 mcg., or isoniazid, 5 mcg., and by the terms of the protocol were excluded from the study.

One original treatment patient on daily isoniazid and sodium para-aminosalicylic acid showed rapid progression at 13 months of drug therapy

FIGURE 2A (PATIENT EW): Low magnification of the wall of the cavity at the site of drainage by a bronchiole. The circular space is an artifact. Isolated tubercles are found adjacent to the wall of the cavity and farther removed from it in the lung parenchyma. Some exudate clings to the cavity wall and extends into the bronchiole. (X6.5)

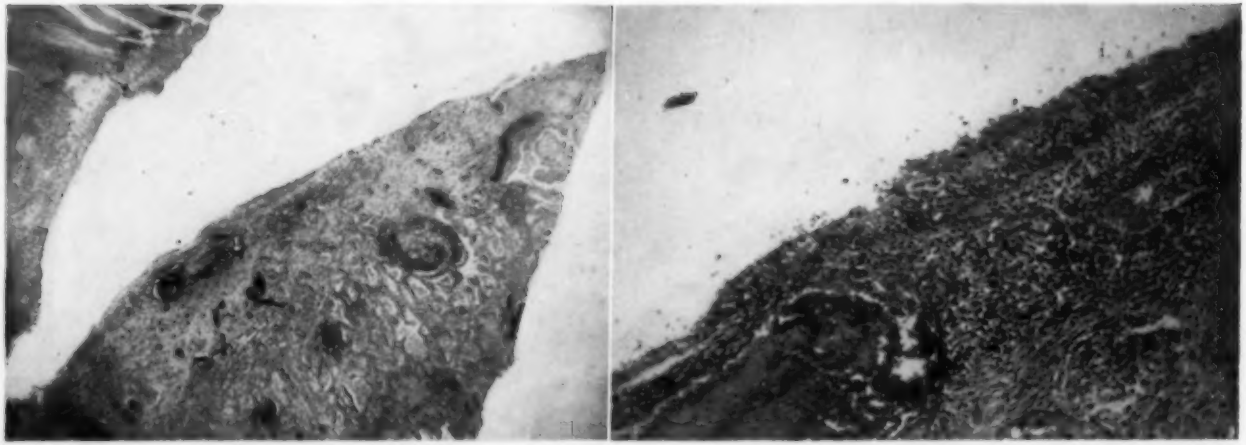

FIGURE 2B FIGURE 2C

Figure 2B (PATIENT EW): Medium magnification of the wall of the cavity beneath some of the exudate. A small part of the cavity has become epithelialized. The wall consists of well vascularized fibrous tissue. One tubercle-like lesion is seen. This consists of epitheloid cells and giant cells, not readily identified at this magnification. The adjacent lung shows pneumonic infiltration, chiefly by large mononuclear leucocytes. (X24)—*Figure 2C*: High magnification of the area shown in Fig. 2B. The lining by epithelium shows infiltration by leucocytes similar to that found in the underlying granulation tissue and more distant fibrous tissue. The tuberculous nature of the inflammatory process is not apparent. (X150)

after initial improvement. Organisms resistant to 10 mcg. of isoniazid appeared in the sputum at the time of worsening and have persisted for four months.

Daily Streptomycylidene Isonicotinyl Hydrazine Sulfate

The daily administration of streptomycyclidene isonicotinyl hydrazine sulfate for meningeal, hematogenous and acute pneumonic tuberculosis was tried for eight patients. For four patients this appeared to prolong life. Through an error, one of these patients, after 191 days of streptomycylidene isonicotinyl hydrazine sulfate, 1.4 grams intramuscularly, failed to receive any therapy for two months at which time progression of hematogenous tuberculosis recurred. Streptomycylidene isonicotinyl hydrazine sulfate 1.4 grams twice daily was then given for 90 days. The patient died at this time. Three patients, acutely ill on admission, died after 90, 67, and 24 days of streptomycylidene isonicotinyl hydrazine sulfate, 1.4 grams daily.

Four others, including one meningitic, were acutely ill on admission. The meningitic received 75 days of therapy with streptomycylidene isonicotinyl hydrazine sulfate 1.4 grams daily has been maintained for 18 months on intermittent therapy without recurrence. Three with acute pneumonic tuberculosis received 60 days of therapy with 1.4 grams of streptomycylidene isonicotinyl hydrazine sulfate daily. All had dramatic clearing of the disease in the chest roentgenogram by the third month.

Four patients given 60 days of streptomycylidene isonicotinyl hydrazine

TABLE IV
ANALYSIS OF DEATHS

Patients	Age	Sex	Hospital Month	Extent of Disease	Duration of Therapy	Cause of Death
			Original SIH Treated			
B.C.	64	M	8	F.A.	7 months	Pulmonary Embolism
W.H.	43	F	1	F.A.	1 month	Tuberculous Meningitis
F.M.	70	M	6	F.A.	5 months	Right Heart Failure
E.G.	36	F	14 days	F.A.	1 injection	Pulmonary Insufficiency
			SIH Prior Therapy			
V.H.	30	F	41	F.A.	12 months	Pulmonary Embolism
J.J.	38	M	43	F.A.	7 months	Cardiac Decompensation
W.J.	54	M	30	F.A.	12 months	Intestinal Obstruction, Postoperative Empyema
J.M.	35	M	23	F.A.	10 months	Pulmonary Embolism
R.P.	53	M	42	F.A.	5 months	Metastatic Carcinoma
			Original Controls			
M.P.	32	F	8	F.A.	7 months	Thrombosis
M.S.	34	F	2	F.A.	2 months	Surgical Shock
			Prior Therapy Controls			
E.J.	21	F	29	F.A.	14 months	Anesthesia
H.S.	58	F	25	F.A.	5 months	Uremia
E.F.	47	F	18	F.A.	8 months	Massive Pulmonary Hemorrhage

PER CENT OF POSITIVE CULTURES RESISTANT TO 1mcg OR MORE OF INAH

ORIGINAL TREATMENT GROUP

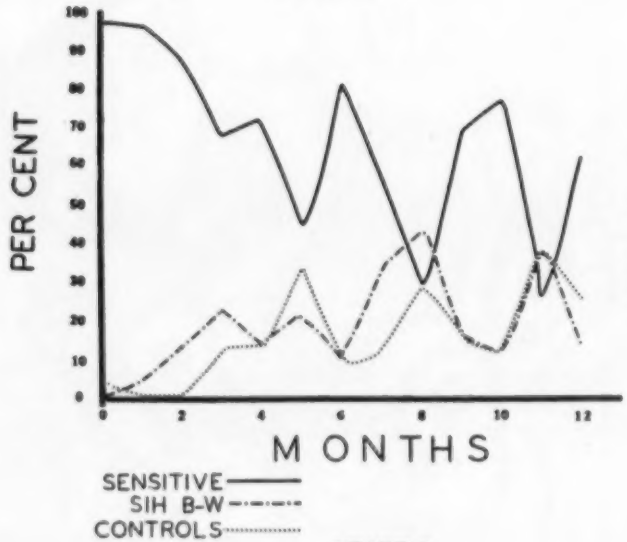

CHART 3

PER CENT OF ALL POSITIVE CULTURES RESISTANT TO 1mcg OR MORE OF INAH

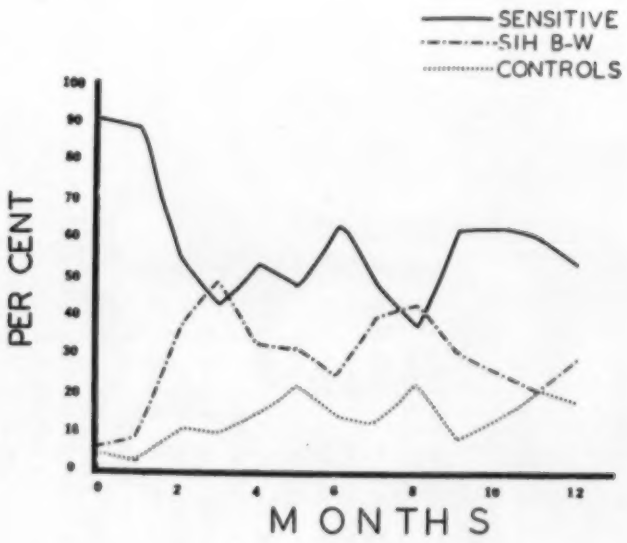

CHART 4

sulfate immediately following acute onset of symptoms showed marked x-ray improvement and rapid cultural conversion. These patients were given 60 days at 1.4 grams daily and are being maintained on daily isoniazid plus daily sodium para-aminosalicylic acid. The films of two patients, one who received 30 days and one who received 60 days of daily streptomycylidene isonicotinyl hydrazine sulfate, are illustrated.

Deaths

Table IV shows deaths occurring by regimens. On no regimen could death be attributed to drug failure. Most were attributable to complications not directly related to tuberculous disease.

Comparative Results of Sputum Cultures

Table V and Charts 1 and 2 demonstrate the results of sputum culture. Cultures were made monthly on Lowenstein-Gentian solid medium. Direct inoculations for sensitivity were made.

TABLE V
RESULTS OF BACTERIOLOGIC EXAMINATION FOR M. TUBERCULOSIS BY MONTHS AND REGIMENS

	ORIGINAL SIH		ORIGINAL CONTROLS		ALL SIH PATIENTS		ALL CONTROLS	
		Per Cent		Per Cent		Per Cent		Per Cent
PRE-TREATMENT								
Number Observed by Culture	30		43		69		62	
Number and Per Cent Positive	17	57	23	53	35	51	34	55
2 MONTHS								
Number Observed by Culture	28		42		66		61	
Number and Per Cent Positive	3	11	5	12	12	18	10	16
4 MONTHS								
Number Observed by Culture	30		43		69		61	
Number and Per Cent Positive	3	10	4	9	13	19	8	13
6 MONTHS								
Number Observed by Culture	29		43		67		61	
Number and Per Cent Positive	7	24	3	7	16	24	5	8
8 MONTHS								
Number Observed by Culture	29		43		67		62	
Number and Per Cent Positive	4	14	3	7	14	21	5	8
10 MONTHS								
Number Observed by Culture	26		41		59		56	
Number and Per Cent Positive	4	15	4	10	9	15	7	13
12 MONTHS								
Number Observed by Culture	23		38		56		50	
Number and Per Cent Positive	4	17	4	11	11	20	6	12

Subscript: The group of 30 patients treated with SIH and the 43 control patients were examined bacteriologically at monthly intervals for the period of 12 months during which they were under observation. Those patients in the groups who remained under observation were compared at the same monthly time periods to determine if there were any statistically significant differences in the proportions in each group showing positive cultures for like time periods. Using the chi-square test with P at the .05 level, there were no significant differences observed for these two groups of patients.

When all patients treated with SIH are compared with all patients on a regimen of isoniazid, streptomycin and PAS, the chi-square test showed significant differences in the percentages of positive cultures at the end of three months, at the end of six months, and again at the end of eight months.

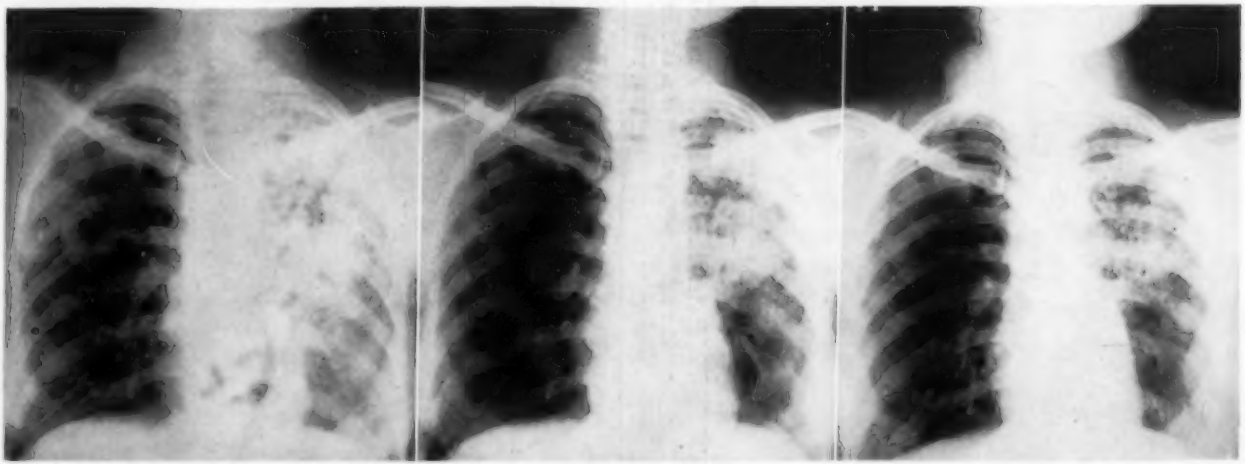

FIGURE 3A FIGURE 3B FIGURE 3C

Figure 3A (PATIENT CG): Chest film of June 18, 1954 showing dense infiltration in left upper one-third with cavity in the mid-lung field. Cultures negative June 21, 1954.—*Figure 3*B: Progress film of July 16, 1954 after 30 days of daily SIH showing clearing. Cultures negative July 16, 1954.—*Figure 3C*: Progress film of September 7, 1954 showing further clearing in both lungs after 60 days on daily SIH. Cultures negative September 10, 1954.

MARKED ROENTGENOGRAPHIC EVIDENCE OF IMPROVEMENT

ORIGINAL TREATMENT PATIENTS

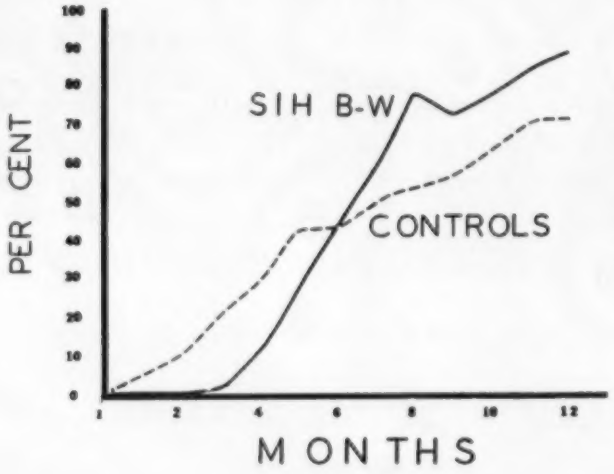

CHART 5

MARKED ROENTGENOGRAPHIC EVIDENCE OF IMPROVEMENT

ALL PATIENTS

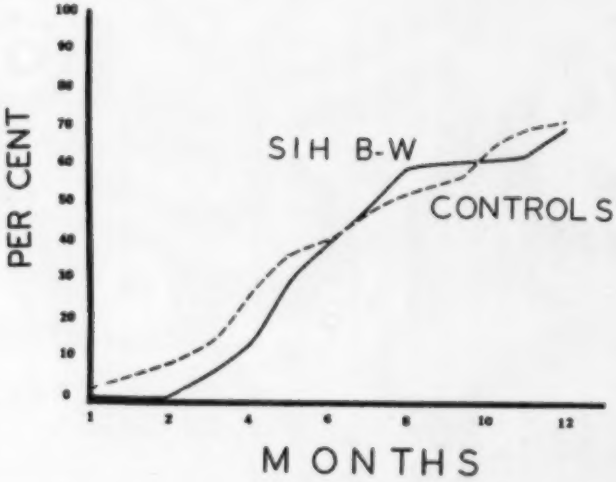

CHART 6

There are no statistically significant differences between the proportion of positive cultures observed for 12 months when original treatment patients are compared. However, when the group of all intermittent streptomycylidene isonicotinyl hyrazine sulfate treated patients was compared to all treated on daily isoniazid regimens, differences favorable to daily isoniazid appear at three, six, and eight months.

The emergence of isoniazid resistant strains on the two regimens is tabulated (Table VI, Charts 3 and 4). The small numbers make interpretation difficult. It is apparent that a small proportion of all patients treated produce isoniazid resistant bacilli on all regimens. When both original treatment and prior therapy patients treated with intermittent streptomycylidene isonicotinyl hydrazine sulfate are compared to all control patients, the proportion of resistant strains seems larger for the inter-

TABLE VI
RESULTS OF CULTURES FOR M. TUBERCULOSIS BY MONTHS SHOWING TOTAL POSITIVE CULTURES, NUMBER AND PER CENT RESISTANT TO DRUG REGIMEN

Months	Total Positive Cultures for SIH Treated and Control Patients	Total Resistant to 1 mcg or more of Isoniazid	Per Cent	Total Positive Cultures for Intermittent SIH Patients	Total Resistant to Isoniazid on Intermittent SIH Regimen 1 mcg or more	Per Cent	Total Positive Cultures in Control Patients	Total Control Patients Resistant to 1 mcg or more of Isoniazid	Per Cent
Original Treatment Patients									
0	40	1	3	17	0	0	23	1	4
1	23	1	4	9	1	11	14	0	0
2	8	1	13	3	1	33	5	0	0
3	9	3	33	6	2	33	3	1	33
4	7	2	29	3	1	33	4	1	25
5	9	5	56	4	2	50	5	3	60
6	10	2	20	7	1	14	3	1	33
7	9	4	44	5	3	60	4	1	25
8	7	5	71	4	3	75	3	2	67
9	6	2	33	2	1	50	4	1	25
10	8	2	25	4	1	25	4	1	25
11	8	6	75	4	3	75	4	3	75
12	8	3	38	4	1	25	4	2	50
All Patients									
0	69	7	10	35	4	11	34	3	9
1	36	4	11	18	3	17	18	1	6
2	22	10	45	12	8	67	10	2	20
3	23	13	57	17	11	65	6	2	33
4	21	10	48	13	7	54	8	3	38
5	19	10	53	12	6	50	7	4	57
6	21	8	38	16	5	31	5	3	60
7	23	12	52	15	9	60	8	3	38
8	19	12	63	14	8	57	5	4	80
9	13	5	38	7	4	57	6	1	17
10	16	6	38	9	4	44	7	2	29
11	15	6	40	9	3	33	6	3	50
12	17	8	47	11	5	45	6	3	50

mittent therapy group. This is undoubtedly due to the addition of the prior therapy patients.

Roentgenographic Evidences of Improvement

Chest roentgenograms taken monthly were available for all patients. These films were compared with the observation film and read by staff concensus as marked improvement, moderate improvement, no change, or moderate or marked worsening. Cavity when present was read for apparent cavity closure.

TABLE VII
CHEST ROENTGENOGRAPHIC CHANGES BY MONTHS* AND REGIMENS

	ORIGINAL SIH		ORIGINAL CONTROLS		ALL SIH PATIENTS		ALL CONTROLS	
		Per Cent		Per Cent		Per Cent		Per Cent
2 MONTHS								
Marked Improvement	0	0	4	9	0	0	4	7
Moderate Improvement	28	90	24	56	41	62	34	56
No Change	3	10	11	26	24	36	19	31
Worsening	0	0	4	9	1	2	4	7
Apparent Cavity Closure	4	14	2	5	5	9	2	4
4 MONTHS								
Marked Improvement	3	10	12	28	8	12	15	25
Moderate Improvement	26	84	22	51	45	68	35	57
No Change	2	6	7	16	12	18	9	15
Worsening	0	0	2	5	1	2	2	3
Apparent Cavity Closure	8	29	10	26	11	20	13	24
6 MONTHS								
Marked Improvement	13	42	18	42	25	38	24	39
Moderate Improvement	17	55	18	42	35	53	29	48
No Change	1	3	6	14	4	6	7	11
Worsening	0	0	1	2	2	3	1	2
Apparent Cavity Closure	12	43	16	42	18	33	20	36
8 MONTHS								
Marked Improvement	24	77	23	53	36	58	32	53
Moderate Improvement	6	19	15	35	19	29	22	37
No Change	1	3	3	7	7	11	4	7
Worsening	0	0	2	5	2	3	2	3
Apparent Cavity Closure	16	57	18	46	22	41	22	39
10 MONTHS								
Marked Improvement	20	77	25	63	34	60	34	63
Moderate Improvement	5	19	10	25	15	26	14	26
No Change	1	3	3	8	7	12	4	7
Worsening	0	0	2	5	1	2	2	4
Apparent Cavity Closure	16	67	18	50	23	50	21	43
12 MONTHS								
Marked Improvement	21	88	25	71	36	68	33	70
Moderate Improvement	3	13	7	20	9	17	10	21
No Change	0	0	2	6	6	11	3	6
Worsening	0	0	1	3	1	2	1	2
Apparent Cavity Closure	16	73	18	58	23	56	21	50

*The data for "Roentgenographic Changes" was originally reported monthly but is here recorded every two months for the sake of brevity.

APPARENT CAVITY CLOSURE

ORIGINAL TREATMENT PATIENTS

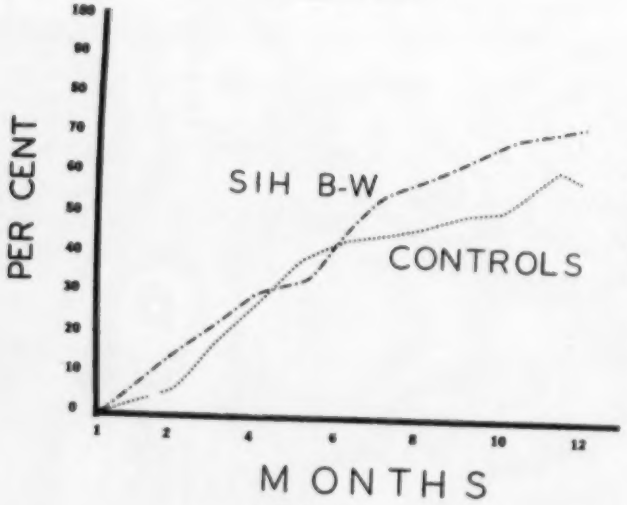

CHART 7

APPARENT CAVITY CLOSURE

ALL PATIENTS

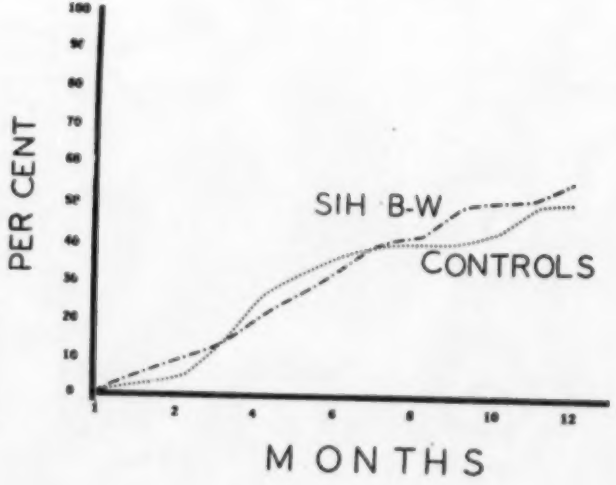

CHART 8

A comparison is shown only between the proportion of marked improvement reported for each regimen (Table VII, Charts 5 and 6). Interpretation of apparent cavity closure is based on comparison of 14 x 17 P.A. films alone (Table VII, Charts 7 and 8).

As before, a significant advantage appears in apparent cavity closure for the original treatment patients on the intermittent regimen. This is not a real advantage since the group of patients originally contained fewer far advanced patients.

When roentgenographic interpretations of marked improvement are compared, it is evident that intermittent streptomycylidene isonicotinyl hydrazine sulfate patients in both original and prior therapy groups seem to improve less rapidly than the controls in the first six months of observation.

Duration of Therapy

In an effort to estimate the comparative effectiveness of the intermittent and daily regimens, the total patient-months of treatment for those reaching the status of "arrested" were calculated as were those for patients accepted for major surgery—resectional or thoracoplasty (Table VIII).

TABLE VIII
PATIENTS REACHING ARREST OF DISEASE OR SURGERY BY MONTHS

	NUMBER	TOTAL PATIENT-MONTHS	MEAN
Patients reaching arrest of disease without major surgery			
Intermittent SIH	35	223	6.3
Controls	36	273	7.6
Patients reaching major surgery			
Intermittent SIH	30	156	5.2
Controls	23	124	5.3

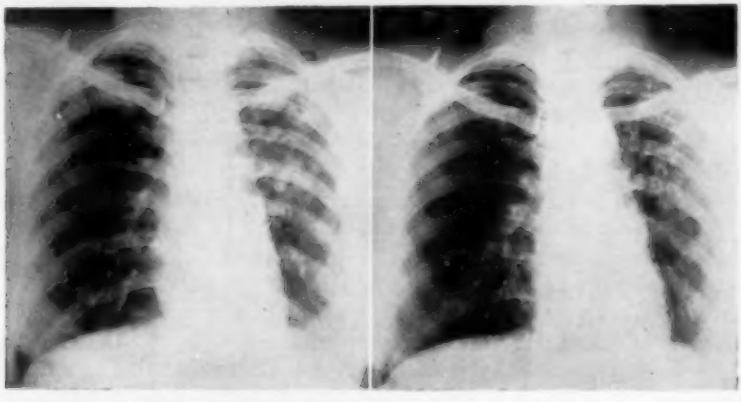

FIGURE 4A FIGURE 4B

Figure 4A (PATIENT CG): Progress film of October 5, 1954 showing further clearing on the right with increasing density of lesions. Cultures of bronchial washings negative October 15, 1954.—*Figure 4B*: Chest film of December 3, 1954 showing clearing and small residual rarefactions (in the original) in the mid-lung field on the left. Cultures of pooled bronchial washings were negative December 10, 1954.

Discussion

The primary object of the present review of our experience with the intermittent administration of streptomycylidene isonicotinyl hydrazine sulfate was to discover whether it constitutes a satisfactory maintenance regimen. It is obvious that it is not as satisfactory as daily regimens when used as a primary therapeutic method for acutely ill patients, for those who have developed bacterial resistance to either drug, or for those who have had prior therapy. Patients treated with intermittent streptomycylidene isonicotinyl hydrazine sulfate showed smaller proportions of marked improvement in radiographic evidences of disease before the seventh month of therapy.

The overall results of prolonged intermittent therapy when compared to those for daily regimens appear to be so slightly less effective that the intermittent use of streptomycylidene isonicotinyl hydrazine sulfate seems practical if used for maintenance of clinical improvement and bacteriostasis.

A recent check of our hospital bedside stands showed that a number of patients cannot be relied upon to take para-aminosalicylic acid unless closely supervised by the ward nursing staff.

Of 55 ambulant patients discharged from the hospital, 12 or 22 per cent were taking oral para-aminosalicylic acid irregularly if judged by their failure to return regularly for prescription refills.

It seems desirable to employ intermittent streptomycylidene isonicotinyl hydrazine sulfate as a maintenance program when it is difficult to rely on patients to take oral drugs regularly, particularly para-aminosalicylic acid.

Streptomycylidene isonicotinyl hydrazine sulfate daily would seem an effective regimen since it seemed to prolong life for patients who were seriously ill at admission. Our present impression is that in acute lesions, especially in young persons not previously treated, daily streptomycylidene isonicotinyl hydrazine sulfate for 30 to 60 days gives *more dramatic and dependable improvement* than is seen among patients who receive isoniazid daily in combination with other drugs.

For a certain number of persons in the more seriously ill category, 10 days of streptomycylidene isonicotinyl hydrazine sulfate was inadequate and the change to intermittent drugs was contraindicated. Daily streptomycylidene isonicotinyl hydrazine sulfate for 30 to 60 days would seem a desirable primary routine where prior treatment failure with either drug is not a problem and the persistence of cavity for long periods of drug treatment before surgery is not anticipated. In our series these cases are not numerous enough for definite comparison. However, the daily use of the two most potent antimicrobials against M. Tuberculosis would seem imminently desirable as a *first therapeutic step* in as much as the most potent drug, isoniazid, is equal to other regimens in daily use when combined with a low-potential-daily-drug such as para-aminosalicylic acid.[4]

It may well be that streptomycin as an initial therapeutic agent in

tuberculosis should be *used daily or not at all* whereas it may be used *intermittently* in combination with isoniazid for the maintainance of bacteriostasis in the period of healing and recovery of general physical efficiency. The toxicity of daily streptomycin, 1 gram up to 60 days, is minimal. With effective bacteriostatis, in combination with isoniazid, emergence of resistant organisms should not be a problem.

SUMMARY

Streptomycylidene isonicotinyl hydrazine sulfate, 1.4 grams intramuscularly when given daily for 10 days and then twice weekly to original treatment patients gives bacteriologic and roentgenographic improvement comparable to that observed for proved regimens over an observation period of 12 months.

X-ray improvement is somewhat slower for streptomycylidene isonicotinyl hydrazine sulfate intermittently treated patients.

This regimen is less effective for patients having had prior therapy with isoniazid or streptomycin or both.

Patients who have had *consistent* isoniazid resistant cultures prior to streptomycylidene isonicotinyl hydrazine sulfate therapy are not especially benefited by streptomycylidene isonicotinyl hydrazine sulfate.

Bacterial resistance to concentrations of 1 mcg. or more of isoniazid develops more frequently among intermittently treated prior-therapy patients but on no regimen was drug resistance considered a significant factor.

Intermittent streptomycylidene isonicotinyl hydrazine sulfate, bi-weekly, may safely be used as a maintenance routine after maximal x-ray and bacteriologic improvement occur. It should only be used *per primum* for patients with a good prognosis who can be expected *not* to require prolonged periods of drug therapy to bring about retrogression of disease.

It is desirable to try daily streptomycylidene isonicotinyl hydrazine sulfate for 30 to 60 days in comparison to daily isoniazid regimens since daily streptomycin has not rigorously been tested in this fashion.

RESUMEN

El sulfato de estreptomicilidene, isonocitol hidracina a la dosis de 1.4 gramos intramuscularmente, fué inyectado a diario por diez días y después dos veces por semana a enfermos no tratados antes, proporcionando una mejoría radiológica y bacteriológica comparable a la lograda con tratamientos ya probados eficaces, por períodos de 12 meses.

La mejoría radiológica es algo mas lenta en los enfermos tratados de manera intermitente.

Este régimen es menos efectivo para enfermos que hayan sido tratados con isoniacida, estreptomicina o con ambas.

Los enfermos que presentan cultivos resistentes a la isoniacida antes de usar la estreptomicilidene isonicotinil hidracida sulfato no se benefician especialmente por ésta.

La resistencia bacteriana a la IMCG o más de isoniacida se desarro lla

más frecuentemente entre los tratados de manera intermitente con anterioridad pero en ningún régimen se consideró que la resistencia a las drogas fuera de importancia.

La droga que motiva esta comunicación puede usarse con seguridad como tratamiento de sostén dos veces por semana una vez lograda la mejoría radiológica y bacteriológica inicial.

Sólo se usará al principio para enfermos con buen pronóstico en los que sea de esperarse que no necesiten largos períodos de tratamiento.

Es deseable ensayar el uso diario de esta droga por 30 a 60 días en comparación con los regímenes de isoniacida puesto que estreptomicina diaria no ha sido probada de esta manera.

RESUME

Le traitement par le "sulfate d'hydrazine isonicotinyl-streptomycylidène" administré quotidiennement à la dose d'Igr. 4 en injection intramusculaire, pendant dix jours et ensuite deux fois par semaine, en association avec le traitement initial des malades, donne une amélioration bactériologique et radiologique comparable à celle observée avec les traitements qui ont fait leur preuve. L'observation a porté sur une période de douze mois.

L'amélioration radiologique est un peu plus lente pour les malades traités par ce produit de façon intermittente.

Cette thérapeutique se montre moins efficace pour les malades qui ont été auparavant traités par l'isoniazide ou la streptomycine, ou par les leux à la fois.

Les malades qui ont eu des cultures résistantes à l'isoniazide avant le traitement par le sulfate d'hydrazine isonicotinyl-streptomycylidène ne sont pas particulièrement améliorés par ce produit.

La résistance bactérienne aux concentrations de I gramma ou plus d'isoniazide, se développe plus fréquemment chez les malades qui ont été traités auparavant d'une façon intermittente mais la résistance ne fut considérée dans aucun type de traitement, comme un facteur déterminant.

Le produit administré d'une façon intermittente deux fois par semaine, put être employé utilement comme un traitement de routine après amélioration radiologique et bactériologique. Il devrait être employé au début chez les malades qui ont un bon pronostic et dont on peut s'attendre à ce que des périodes de traitement prolongées ne soient pas nécessaires pour amener la régression des lésions.

Il est souhaitable d'essayer le sulfate d'hydrazine isonicotinyl-streptomycylidène pendant un à deux mois par comparaison avec le traitement par l'isoniazide quotidien, puisque le traitement quotidien par la streptomycine n'a pas été expérimenté avec rigueur de cette manière.

ZUSAMMENFASSUNG

Streptomycyliden-Isonicotinylhydrazin-Sulfat erzielt bei einer Dosierung von 1,4 g intramuskulär täglich, zehn Tage lang und dann zweimal wöchentlich, bakteriologische und röntgenologische Besserungen, die bei einer Beobachtungszeit von zwölf Monaten mit den Besserungen nach

anderer erprobter Kombinationstherapie zu vergleichen sind.

Die röntgenologische Besserung erfolgt bei den mit Streptomycyliden-Isonicotinylhydrazin-Sulfat intermittierend behandelten Patienten etwas langsamer.

Dieses Medikament ist weniger wirksam bei Patienten, die schon vorher eine Behandlung mit Isoniazid oder Streptomycin oder mit beiden Medikamenten zusammen erhalten hatten.

Patienten, die vor der Streptomycyliden-Isonicotinylhydrazin-Sulfat-Behandlung isoniazid-resistente Kulturen hatten, erfuhren durch die Streptomycyliden-Isonicotinylhydrazin-Sulfat-Behandlung keine besondere Besserung.

Bakterienresistenz gegen *IMCG* oder noch mehr gegen Isoniazid entwickelt sich häufiger unter den intermittierend behandelten Patienten, die schon vorher eine Chemotherapie erhalten hatten; aber bei keinem Behandlungsschema wurde die Bakterienresistenz als entscheidender Faktor angesehen.

Intermittierende Behandlung mit Streptomycyliden-Isonicotinyl-hyrazin-Sulfat kann ohne weiteres als eine Erhaltungstherapie nach möglichster röntgenologischer und bakteriologischer Besserung weitergeführt werden. Die *primäre* Anwendung dieses Präparates sollte nur Patienten mit guter Prognose vorbehalten werden, bei denen erwartungsgemäss *keine* längeren Behandlungszeiten erforderlich sind, um eine Rückbildung der Krankheit zu erreichen.

Es ist anzustreben, Streptomycyliden-Isonicotinylhydrazin-Sulfat 30-60 Tage lang täglich zu geben, um einen Vergleich mit dem Isoniazid-Behandlungsschema bei täglicher Verabreichung zu haben, da tägliche Gaben von Streptomycyliden-Isonicotinylhydrazin-Sulfat in dieser Art noch nicht gründlich versucht wurden.

Acknowledgement: The observations of Marie Lewis, R.N. and the "Nursing Team for Antimicrobial Therapy" contributed vitally to the accuracy of this study.

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The Superior Vena Caval Syndrome: Report of 21 Cases

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The purpose of this paper is, to review the literature in regard to the anatomy, etiology, diagnosis and treatment of the superior vena caval syndrome, and to present 21 cases admitted to the Los Angeles County General Hospital between 1947 and 1954.

Superior vena caval obstruction probably dates back to the beginning of disease, but it was not until 1757 that Willian Hunter published the first authentic account of a case which resulted from aortic aneurysm.[1] Since then over 500 cases have been reported by various authors, and doubtless hundreds more have been unreported, unrecognized, or were only partial obstructions. The youngest patient recorded was a two month old baby with spontaneous pneumothorax, and the oldest was a 93 year old man with thrombosis of the superior vena cava with extensive collateral circulation.[2] Although superior vena caval obstruction has been relatively uncommon in general practice (Hinshaw found four cases in 85,000 consecutive admissions to the White Memorial Hospital in Los Angeles prior to 1947), it is wise to keep this syndrome in mind for its beginnings may be masked by other more obvious conditions.

Anatomy: Functionally, the superior mediastinum through which the superior vena cava passes is the busiest transportation route in the body, for through it goes all the air which enters or leaves the lungs, all the food which enters the stomach, all of the lymph which enters the thoracic duct, and all the blood which leaves the heart via the aorta or returns to it via the superior vena cava from the upper half of the body.

Anatomically, the superior vena cava is approximately seven centimeters in length extending from the junction of the right and left innominate veins superiorly, to the right auricle inferiorly. The azygos vein enters just above the pericardial reflection, and the last two centimeters of the cava lie intrapericardially. The vena cava is one of the most compressible structures in the area, having soft thin walls and a low pressure. It is situated between the rigid bony anterior chest wall anteriorly; the pulsating muscular walled ascending aorta anteromedially; the relatively rigid cartilaginous trachea and right bronchus posteriorly; the soft expandable pleura and right lung laterally; and groups of potentially expanding lymph nodes anteriorly (right anterior mediastinal), posteriorly (right laterotracheal chains), and infero-posteriorly (right bronchial nodes and tracheal bifurcation nodes). In addition it is in close relation to the right pulmonary and innominate arteries, the phrenic nerve which courses over its right lateral surface, and the thymus near its anteromedial surface.

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Etiology and Pathogenesis: There are four major causes of obstruction, namely; tumors, aneurysms, mediastinitis, and phlebitis with thrombosis. Among the minor causes may be listed such events as trauma, pericarditis with constriction of the pericardial ring, leukemia, mitral stenosis, pneumothorax, mediastinal emphysema, and about 10 per cent due to undetermined causes.

The usual age affected is the 30-60 year group, which coincides with the range of neoplasms, late syphilis and arteriosclerosis. Men are predominantly affected in a ratio of 4:1 due to the incidence of aneurysms, bronchogenic carcinoma and malignant lymphomas in the male. Bronchogenic carcinoma is now second only to gastrointestinal carcinoma, and superior vena caval obstruction has been estimated to occur in about 10-15 per cent of these.[3, 4]

Tumors account for over 40 per cent of cases of obstruction with the percentage climbing recently due to a marked increase in bronchogenic carcinoma, a greater population of elderly persons with a corresponding increase in tumors, and a decrease in infectious processes. The main action of tumors on the vena cava is by external compression by the tumor itself or by invaded lymph nodes, occasionally by intraluminal invasion and rarely by thrombosis except with partial occlusion first.

The most common tumor involving the superior vena cava is bronchogenic carcinoma, 80 per cent of which are right bronchial in origin and 90 per cent of which are of a highly malignant, rapidly growing anaplastic type.[4] Metastases to adjacent lymph nodes, metastatic tumor from other sources, malignant lymphomas and other malignant neoplasms belong in this group in which the prognoses is generally hopeless.

Falling in the tumor classification but with considerably better prognosis, are the benign tumors, cysts, mediastinal lymphadenitis, enlarged thyroid or thymus, tuberculomas, syphilitic gummas and other granulomas. However benign tumors account for only 7 per cent of the tumor involvement while 93 per cent is caused by malignant varieties.[1]

Aneurysms have been found to cause about 25 per cent of the cases of obstruction, compressing or rupturing into the vena cava. Although luetic aneurysms have been a prime factor in the past, the incidence is gradually decreasing due to improved and intensive therapy. Arteriosclerotic dissecting aneurysms however are on the increase due to increasing longevity of the population. Rose[5] has estimated that 70-85 per cent of all obstructions are caused by tumors or aneurysms.

Mediastinitis has caused about 12 per cent of obstructions and shows a slight increase in incidence. Initiating factors are those common to the chest cavity such as infections, inflammations or trauma which may have occurred years ago or which may have initiated a relatively indolent lymph node infection and abscess from lung lymphatic drainage. Chronic fibrous mediastinitis is thus produced, causing a fibrotic, collagenous mass with cicatricial scarring in the superior mediastinum and consequent occlusion of the superior vena cava.

Thrombosis has caused about 13 percent of vena caval obstruction;

36 per cent of which have been due to phlebitis listed as idiopathic, syphilitic, tubercular, pyogenic and traumatic; 29 per cent were due to external compression; 23 per cent were due to mediastinitis; and 10 per cent were unknown.[2, 6]

Diagnosis is made by history, physical examination and laboratory studies and the findings will depend on 1) the degree of occlusion, 2) the rapidity of development, 3) the presence or absence of collateral circulation.[7]

History elicits such symptoms as headache, shortness of breath, buzzing in the ears, swelling of the neck and face, bulging eyes, deafness, somnolence, machinery-like noise in the head, epistaxis and rarely hemoptysis.

Physical examination reveals a patient with painful edema and peculiar reddish cyanosis of the upper half of the body, and paleness of the lower half. Cyanosis and edema are aggravated by the horizontal position and relieved by the upright position. Collateral circulation is pronounced in the four classical collateral routes as follows:[3]

1. Azygos, including the main and accessory azygos veins, ascending lumbar veins, lumbar veins and iliacs. The route is most important when the obstruction is above the azygos.
2. Internal mammary, leading to the superior and inferior epigastrics, external iliac and inferior vena cava.
3. Lateral thoracic, going via the thoracoepigastric, superficial epigastric, superficial circumflex iliac veins, thence to femoral and inferior vena cava. These are the most commonly seen superficial collaterals.
4. Vertebral, which is a deep system including the intervertebrals, innominate, dural sinuses, intercostals, lumbars, and sacrals.

Laboratory studies reveal marked increase in venous pressure (above 150 mm. citrate) in the upper extremities while the lower extremities are a normal 50-150 mm. pressure or may even be decreased. Pressure readings are taken from the antecubital vein with a 3-way stopcock spinal manometer using 2.5 per cent citrate solution.[3] An exercise test has been described by Hussey, et al[8] in which the patient opens and closes his fist forcefully for one minute while venous pressure readings are being made. In superior vena caval obstruction the citrate pressure will rise 10 cm. or more as a result and then gradually recede to normal, whereas in a normal individual it remains constant. Paradoxical pressure in relation to breathing has also been noted in which the column rises with inspiration and lowers with expiration if the obstruction is below the azygos vein. Another test, which has questionable value, is the lower chest tourniquet test in which a tourniquet constricts the superficial thoracic collaterals and raises the venous pressure if the obstruction is below the azygos vein. Circulation time is usually prolonged with obstruction.

Infra-red photography demonstrates abundant superficial collaterals on most patients.

Phlebography is a standard procedure, not only for demonstration of collaterals but for localizing the site of obstruction and giving a clue

as to the cause. For this, 30 cc. of 35 per cent or 70 per cent diodrast or thorotrast is injected into any vein — usually antecubital or jugular — and serial x-ray films are taken simultaneously. Aneurysms of the arch of the aorta causes displacement and compression of the superior vena cava, while obstruction due to malignancy causes distal dilatation *in situ*.[9] Roentgenograms usually show the mass in the superior mediastinum if due to a tumor process. Mediastinography as reported by Berman et al[12] may also prove to be a boon to diagnosis and localization of mediastinal masses.

Treatment and prognosis at the present time are relatively poor. Approximately 85 per cent are terminal, due to malignancies or aneurysms and only palliation can be offered. Symptomatic relief may be obtained by repeated phlebotomies, decompression if due to external pressure only, administration of oxygen, ACTH, and diuretics, lumbar puncture to relieve intracranial pressure, and roentgen ray and nitrogen mustard therapy. The two latter modalities have been found worthwhile by Roswit et al[4] in 76 per cent of patients with inoperable bronchogenic carcinoma, giving remissions up to one year with roentgen rays alone and up to five months with nitrogen mustard alone. Without treatment death usually resulted in 10 weeks or less. The hardest available x-rays were given daily at doses of 75-100 r and as improvement was noted the dosage was increased gradually to 250 r daily and maintained until maximum clinical benefits were attained. A total dosage of 1000-5000 r was delivered through at least two portals with an average optimum dosage of 3500-4500 r being considered most efficient. Nitrogen mustard was given intravenously in running infusion to other patients, 0.1 mg/Kg. body weight with sedation, for four consecutive days. Results in these patients were less satisfactory than those given x-ray treatment. In both the series treatment was temporarily life-saving and made the patient more comfortable, but was still only palliative.

Death occurred as a result of cerebral anoxemia, failure of respiratory centers or strangulation edema of the glottis and respiratory passages.

For other causes of obstruction, treatment is directed toward the underlying cause such as: antisyphilitic therapy if there is syphilitic mediastinitis, chemotherapy and antibiotics if due to pyogenic or inflammatory sources, anticoagulant therapy if due to thrombosis, and surgery to restore the patency of the venous channel.

Indications for surgery[2] are to remove benign tumors, release fibrous bands and adhesions, decompress the mediastinum if markedly obstructed or rapidly increasing, which may be a temporary life-saving operation, and to resect the occluded vena cava and replace it with a vein or arterial graft for what is hoped will be a more permanent life-saving operation.

Scannell and Shaw[10] have described their recent results with vein grafts with apparently good function. Holman and Steinberg[11] have also written of their successful anastomosis of an arterial graft from a blood vessel bank in a 26 year old patient. The graft was anastomosed between the atrial stump of the occluded vena cava and the right innominate vein. Occlusion

in this patient was due to fibrotic mediastinal lymphadenitis. Recovery was excellent and 10 months following surgery the patient was still doing well with no symptoms. Arterial graft was chosen because it was not so subject to post operative fibrosis, it was more rigid, and less easily compressed than were vein grafts. However, homogenous or autogenous veins can be used if arterial grafts are not available, but they tend to collapse and thrombose.

For patients with good collateral circulation the best treatment is to do nothing but possibly restrict activity, for they get along nicely.

For those with poor collateral however, who are in the benign group, surgery is indicated and especially so with increased knowledge of vessel grafting and chest surgery.

Case Presentations: In presenting the following cases, it is not with the idea that they are all classical text-book pictures such as has been described, but they represent an average series of patients such as might be seen in a large hospital. Some have been signed out with a diagnosis of superior vena caval syndrome, but there was insufficient evidence recorded on the charts to warrant such a diagnosis. These have not been included. It may well be doubted whether some of the cases actually had superior vena caval obstruction or only partial or even innominate, subclavian or carotid obstruction. None had as complete a battery of diagnostic tests as would be desirable from an academic viewpoint. However, the significant point is that the doctors in charge of the patient (interns, residents and attending staff) recognized that some degree of superior vena caval syndrome existed as evidenced by extensive trunk collateral with downward flow of blood and swelling of the arms, neck and face. The full-blown classical picture of any disease is a rarity while mild to moderate manifestations are commonplace. (See Chart)

The patient age ranged from 41 to 83 years with an average of 59 years at the beginning of symptoms. Fifty-seven per cent were men.

Clinical evidence of superior vena caval obstruction was made on the basis of swelling of the neck, face and arms, and extensive venous collateral circulation over the chest and abdomen with downward flow of blood. In addition, 39 per cent had shortness of breath and upper extremity cyanosis. Arm venous pressure readings were taken on eight (37 per cent) with a range of 250-800 mm. saline and an average of 386 mm. Only four lower extremity pressure readings were taken with an average of 165 mm. saline.

Arm to tongue circulation time using "Decholin" was done in six with a range of 7-120 seconds with an average of 34 seconds. Arm to lung time using ether was done in three averaging seven seconds.

Angiograms were done on four which illustrated superior caval obstruction or innominate obstruction.

Roentgen-ray therapy was given to five, all but one of whom lived over six months and one of whom was placed in a home with complete remission after six months and has not been followed.

Six (29 per cent) were discharged, four having remission of symptoms

Case No.	Age	Sex	Collat. Circ.	Edema Upper Extrem.	Dyspnea	Arm Venous Pressure mm. Saline	Leg Venous Pressure mm. Saline	Arm-tongue Circ. Time, Seconds	Arm-lung Circ. Time, Seconds	Angiogram Evidence	No. X-Ray Film Rx Given	Etiology Bronchogenic Ca.	Thyroid	Aortic Aneurysm	Undiagnosed	Duration S. & S.	Death	Autopsy	Death Certificate Diagnosis or Other Comments
1.	68	M	x	x	x	320					6	x				1 mo.	x	x	Ca. of lung with Sup. V. C. Syndrome
2.	47	M	x	x								x				1 wk.	x		Bronchogenic Ca.
3.	67	M	x	x	x							x				1 wk.	x	x	Bronchogenic Ca.
4.	49	F	x	x											x	6 yr.			Spontaneous remission
5.	63	F	x	x		250	150	22	3				x			2 mo.	x	x	Congestive heart failure Pulmonary embolism, ASHD
6.	44	M	x	x				19				x				1 mo.	x		Resp. failure & Pulm. edema
7.	83	F	x	x									x			3 mo.			Pt. did not return
8.	62	M	x	x	x									x		1 yr.	x		Anoxia, tracheal compression & luetic aneurysm asc. aorta
9.	68	F	x	x		270	240			x					x	5 yr.			No progression, Home
10.	67	M	x	x							18	x				6 mo.	x		Died out of Hosp. Biopsy Dx was Oat Cell Ca.
11.	54	F	x	x											x	4 mo.	x		Prob. Cerebral thromb. due to Sup. V. C. Obstruction
12.	50	F	x	x	x	310		16		x	28				x	6 mo.			Home. No evid. of obstr.
13.	65	M	x	x								x				1 wk.	x	x	Empyema & Pneumonia, Br. Ca.
14.	41	F	x	x		390		120	16						x	6 yr.			Discharged against advice
15.	66	M	x	x	x							x				2 wk.	x	x	Sup. V. C. Obstr & Throm. due to Br. Ca.
16.	52	F	x	x	x	800		7	4	x					x	1 da.			Pt. came for angiogram only
17.	76	M	x	x	x							x				2 wk.	x		Pancoast tumor (Bronchogenic Ca.)
18.	45	M	x	x							?			x		18 mo.	x		Died at home. X-Ray Rx outside. Dx at tumor surgery at LACGH
19.	51	F	x	x							?	x				7 mo.	x	x	Sup. V. C. Syndrome due to Pleomorphic Br. Ca.
20.	69	M	x	x		300	160	21				x				10 mo.	x		Death due to Br. Ca.
21.	60	M	x	x		450	130			x		x				2 mo.	x		Sup. V. C. Obs. due to Br. Ca.
Tot.		12M	21	21	8	8	4	6	3	5	5	11	2	2	6		15	6	(Total No. of patients)
Avg.	59	57%	100%	100%	39%	386	165	34	7	24%	17	53%	9%	9%	29%	3 mo.	72%	48%	(2 patients died out of hospital)

or no progression, one was discharged without consent and one entered only for angiogram studies.

Surgery was attempted on only one, who had an undiagnosed aortic aneurysm.

Etiology of the total number of cases was found to be: bronchogenic carcinoma, 53 per cent, aortic aneurysm, 9 per cent, substernal thyroid, 9 per cent, and undiagnosed mediastinal tumors, nodes, granulomas, etc., 29 per cent. However, of the patients who died, over 72 per cent of the caval obstructions were due to bronchogenic carcinoma, 14 per cent to aneurysm and 7 per cent undiagnosed and 7 per cent to thyroid. The number having caval or innominate thrombosis was not recorded in this series as it was generally secondary to some other process and not a primary cause of obstruction.

Autopsy was done on only 48 per cent of those who died in the hospital (two died outside), but only one of these was not diagnosed with certainty at the time of death.

Conclusions

From this small series of cases we notice some definite trends.

1. Sex ratio is equalizing (57 per cent men in this series as compared to 75 per cent in literature review).
2. Age is increasing (average of 59 years in this series).
3. Bronchogenic carcinoma is an increasing cause of caval obstruction causing 72 per cent of deaths.
4. Average venous pressure in arms exceeds that in legs by over 200 mm. saline.
5. Prognosis may be favorable if obstruction is not due to bronchogenic carcinoma or aortic aneurysm.

SUMMARY

A review of the anatomy, etiology, diagnosis and treatment of the superior vena cava syndrome is presented. The major etiologic factor is bronchogenic carcinoma, 10-15 per cent of which have superior vena caval obstruction with generally hopeless prognosis. With increased knowledge and use of vessel grafting, prognosis is brighter for those with non-malignant and non-aneurysmal obstruction.

Twenty-one cases entering Los Angeles County General Hospital between 1947-1954 are presented. Fifty-seven per cent were men at average age of 59; seventy-two per cent of deaths were due to bronchogenic carcinoma.

RESUMEN

Se presenta una revisión de la anatomía, etiología, diagnóstico tratamiento del síndrome de vena cava superior. El factor etiológico más importante es el carcinoma broncogénico, el 10 al 15 por ciento de los cuales presenta obstrucción de vena cava superior, dando un pronóstico sin esperanzas. Con el acerbo de los conocimientos y el uso de los injertos de vena, el pronóstico es mejor para aquéllos de etiología no maligna ni aneurismática.

Veinte uno casos que entraron al Los Angeles County General Hospital

entre 1947 y 1954 se presentan. El cincuenta y siete por ciento eran hombres en una edad promedio de 59 años; el setenta y dos por ciento de las muertes fueron debidas a carcinoma bronquiogénico.

RESUME

L'auteur présente une revue générale de l'anatomie, de l'étiologie, du diagnostic, et du traitement du syndrome de veine cave supérieure. Le fecteur étiologique principal est le cancer bronchique. 10 à 15% d'entre eux provoquent une obstruction de la veine cave supérieure, avec généralement un pronostic sans espoir. Grâce aux connaissances accrues et à l'emploi de greffes des vaisseaux, le pronostic est meilleur pour les obstructions qui ne sont ni de nature cancéreuse ni de nature anévrysmale.

L'auteur présente 21 cas admis à l'Hôpital Général du Comté de Los Angeles, entre 1947 et 1954. 57% concernent des hommes dont l'âge moyen est 59 ans. 72% des décès sont imputables au cancer bronchique.

ZUSAMMENFASSUNG

Es wird ein Überblick über die Anatomie, Ätiologie, Diagnose und Behandlung des oberen Vena cava-Syndroms gegeben. Für die Ätiologie am wichtigsten ist das bronchogene Karzinom, wobei in 10%-15% der Fälle von Verengung der oberen Vena cava im allgemeinen eine hoffnungslose Prognose besteht. Die Prognose wird bei Patienten mit nicht maligner und nicht auf einem Aneurysma beruhender Verengung infolge zunehmender Kenntnis über die Erkrankung und durch die Vornahme von Gefässtransplantationen besser.

Es wird über 21 Fälle des Los Angeles County General Hospital aus der Zeit zwischen 1947 und 1954 berichtet. 57% der Fälle waren Männer mit einem Durchschnittsalter von 59 Jahren; 72% der Todesfälle waren dem bronchogenen Karzinom zuzuschreiben.

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Therapeutic Aspects of Pulmonary Emphysema*

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The emphysema patient who suffers a bronchospastic crisis represents one of the most trying situations with which we, as physicians interested in chest diseases, are confronted. The allergic approach in most patients with pulmonary emphysema has proved to be so disappointing generally that many physicians are inclined to omit completely a serious evaluation of allergenic possibilities. Certainly even the partial conquest of the allergic bronchospastic component is cogent and a careful survey for potentially significant extrinsic offenders followed by desensitization may be fruitful in a small percentage of patients.

It is always important to bear in mind that people with emphysema have physiological derangements which are seriously compromised secondary to superimposed bronchospastic difficulties. Therefore, a few cardinal principles are worthy of review:

1) Adequate gas exchange, which takes place at the alveolar level, requires *effective alveolar* ventilation. There is an enormous quantitative difference between two individuals, each exhibiting a minute volume of 10 liters per minute—one of whom has a tidal air of 500 cc. who breathes 20 times per minute, and the other who breathes 40 times a minute with a tidal air of 250 cc. The significant difference lies in the consideration of the anatomical dead air space, which ordinarily is approximately 150 cc. for adult males. *Effective* alveolar ventilation in the first instance would be 500-150 cc. (the volume of the anatomical dead air space) or 350 times 20 breaths per minute, which equals 7000 cc. per minute; whereas in the second case we would have 250-150 cc. times 40 breaths per minute, which equals 4000 cc. per minute. Obviously there is a tremendous quantitative difference between 4000 and 7000 cc. of effective ventilation per minute. Based on this consideration, tracheotomy may be indicated in desperate situations, the purpose of tracheotomy being to diminish the volume of the anatomical dead air space as well as for suctioning secretions in such cases.

2) Many emphysema patients already exhibit varying degrees of diminished arterial oxygen saturation with or without an increase in the partial pressure of carbon dioxide in the arterial blood. The net effect of superimposed bronchospastic difficulties is to aggravate the existing degree of lowered arterial oxygen saturation and hypercapnia by diminishing further the ingress of oxygen and the egress of carbon dioxide. This circumstance is referred to as alveolar hypoventilation.

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3) When one speaks of diminished arterial oxygen saturation, there is the additional problem of alveolo-capillary block. The syndrome of alveolo-capillary block is not merely a manifestation of thickening of the alveolar membrane, but embraces the problem of diminished total *functioning* alveolar membrane available for gas exchange. The presence of any type of fluid within the alveolus which interferes with effective gas exchange is part and parcel of the alveolo-capillary block syndrome.

Apropos the discussion at hand, there is no question but that disruption of normal alveoli leads to diminished surface area available for gas exchange. Furthermore, asthmatic difficulties are frequently attended by an increase in mucus secretion which aggravates the existing degree of alveolo-capillary block. Add to this complex atelectasis secondary to inspissated mucus and one has a further increase in the venous admixture returning to the left side of the heart over and above any pre-existing level.

4) Anxiety commonly increases the degree of pre-existing bronchospasm.

5) Fever, which may be due to drug reaction, bronchial or pulmonary infection, at times associated with atelectasis, increases the tissue requirements for oxygen, which are already compromised. The work of breathing is also increased.

6) But hanging like the Sword of Damocles over this whole array of happenings is the spectre of hypoxia in the emphysematous patient. Cournand and other workers have demonstrated that even moderate degrees of anoxia have a constrictive effect on the pulmonary vascular bed, which results promptly in the development of pulmonary hypertension. This of course imposes a strain on the right ventricle which may result in right heart failure. Anoxia and cor pulmonale are frequently responsible for the development of polycythemia and hypervolemia, which in turn invoke an additional burden on the circulation, enhancing the pre-existing degree of right ventricular strain.[1]

It now becomes obvious that a respiratory complication in the emphysematous individual increases the work of breathing, it reduces alveolar ventilation below pre-existing levels, it may increase the degree of alveolo-capillary block, it may increase the venous admixture returning to the left side of the heart, it may decrease arterial oxygen saturation and increase the degree of hypercapnia—all resulting in ingravescent pulmonary hypertension and in a potential breakdown of compensatory mechanisms preserving the maintenance of a normal pH.

At this point, we shall apply some of these principles to the medical management of the emphysema patient with super-imposed bronchospastic difficulties. Several DON'Ts are in order:

1) Don't use morphine and atropine. This point cannot be over-emphasized. Morphine is a broncho-constrictor and atropine dries pulmonary secretions. Furthermore, morphine, which depresses the central nervous system, specifically dulls the respiratory center. There are those who use meperidine (Demerol) sparingly. Chloral hydrate is effective as a sedative but it must also be used with caution.

2) Don't abuse oxygen. In advanced pulmonary emphysema the level of hypercapnia may be so great that the respiratory center no longer responds adequately to increases of carbon dioxide in the blood. Oxygen therapy may result in decreased ventilation, which increases carbon dioxide retention. This may rapidly lead to a breakdown of the acid-base relationship, which eventuates in uncompensated respiratory acidosis and its grave sequelae. This doesn't mean that oxygen is contraindicated in the treatment of pulmonary emphysema, but it does indicate that oxygen should be used with caution and under careful supervision by physicians and nurses who are acquainted with the hazards of oxygen therapy in the emphysema patient.

3) Above all, don't palliate in the face of a desperate situation. Time is of the essence and a positive approach utilizing sound measures simultaneously may be mandatory.

Therapeutic approach to the patient with pulmonary emphysema and superimposed bronchospasm:

1) Bronchodilators such as isopropylepinephrine (Isuprel) and racemic epinephrine hydrochloride (Vaponephrin) are of value in improving alveolar ventilation and thereby promoting carbon dioxide elimination. Since cholinergic impulses exert a bronchospastic effect, it is logical that anticholinergic drugs be considered. Good spasmolytic effect without side reaction has been reported by Segal,[2] Seabury[3] and others. They have used Methscopolamine bromide (Pamine) as an aerosol in doses of 0.22 and 0.33 mgs. per cc. Barach recently reported using diphenmethanil methylsulfate (Prantal) by injection with measured improvement of ventilation.[4] It is well to familiarize oneself with these approaches since some patients appear to become refractory to sympathomimetic agents. Aminophyllin given intravenously is a dependable bronchodilator.

2) Oxyethylated tertiary octylphenol-formaldehyde polymer (Alevaire) is frequently used to decrease the viscosity of bronchial secretions. Although this preparation may be used effectively, some patients exhibit an increase in the degree of bronchospasm while receiving this form of therapy. Secretory expectorants should be used routinely. Where potassium iodide is poorly tolerated, one may use a guacolate preparation.

3) The graver the problem, the greater the indication for the use of antimicrobial therapy even prior to the availability of culture and sensitivity reports. Adjustments may be made within 24 hours if necessary. We include nitrofurantoin (Furadantin) in the group of drugs to be used for sensitivity determination, particularly when secretions are obviously purulent. Furadantin may be quite effective in the presence of pseudomonas infection. Many physicians utilize antibiotic aerosols while others prefer the conventional methods of drug administration.

4) Much has been written during the past several years concerning the virtues of intermittent positive pressure breathing in the management of pulmonary emphysema. To be most effective this should be combined with bronchodilator aerosols. Apparatus, which incorporates positive pressure breathing with exsufflation and high negative expiratory pressure,

would appear to have some advantage in some cases over the usual form of IPPB/I. At the appropriate time diaphragmatic breathing exercises may be helpful in improving pulmonary ventilation. Apparently, patients learn the technique reasonably well if they are tilted slightly in the head-down position with a sand bag applied to the abdomen.

5) Although ACTH and Cortisone have been used effectively in many instances, the hazards incurred with these agents are well known to all. The advent of metacortandracin (Meticorten) has broadened the possibilities of steroid therapy because this preparation does not cause sodium and fluid retention or potassium depletion. Barach[4] has reported favorable results which have been confirmed by other observers. The average initial dose is approximately 50 mg. daily for one to three days until symptomatic improvement occurs. Thereafter the dose may be halved and a maintenance dose of 10 to 20 mg. daily continued. Since upper gastrointestinal tract ulceration and/or perforation are not uncommonly encountered among patients taking Meticorten[5] it has been suggested that all patients on this preparation be given the benefit of intermediary feedings and antacid preparations routinely.

6) The more seriously ill the patient, the greater the need for caution in the amount and frequency of sedation administered, particularly if coupled with oxygen therapy. We have already stated that oxygen is indicated in the hypoxic patient. In general it is advisable to begin with lesser amounts of oxygen, preferably one liter per minute by nasal catheter increasing the rate of flow by increments of one liter at intervals of 12 to 24 hours as indicated until a maximum of seven liters is attained. At the appropriate time, patients should be weaned away from oxygen over a period of several days.

7) Those who are in congestive heart failure should be treated with digitalis and other measures as required. The proper place of acetazolamide (Diamox) as a therapeutic agent in this condition is still not clear.

8) Venesection is indicated whenever the hematocrit exceeds a level of 52 per cent. Venesection reduces the blood volume and the degree of polycythemia.

9) Pneumoperitoneum still has its advocates and its detractors. There can be no doubt that it has been beneficial in a certain percentage of patients suffering with pulmonary emphysema. Perhaps those who have had broad experience utilizing this measure properly in a large sample of patients have more cause for enthusiasm than others. It must be borne in mind that the volume of air per refill and the frequency of refills are quite different here than for the tuberculous patient. The objective of pneumoperitoneum is to introduce only sufficient air to permit the diaphragm to enter again into the mechanical ventilatory process. Barach has indicated that an elevation of two inches suffices.[6] Excessive amounts of air impede ventilation.

At this juncture I should like to speculate for a moment. Anatomically the diaphragm is a musculo-tendinous structure. Even normally, we un-

derstand that the proportion of muscle and tendon varies considerably. The muscular component is striated muscle which complies with the law of stretch-hypertrophy. Conversely, the muscle fibers may well atrophy with disuse. Is it not conceivable then that disuse atrophy of the diaphragm secondary to long-standing pulmonary over-distention could be reversible or irreversible? Might that not explain, at least in part, why some patients benefit from pneumoperitoneum and some do not? Then again, the success or failure of pneumoperitoneum therapy may possibly be related to lung compliance. A rigid lung may not respond to pneumoperitoneum whereas a supple lung may. I have observed patients whose diaphragm following the first insufflation of air appeared flaccid and ineffectual, but who some weeks later exhibited strong diaphragmatic contractions. In my experience these are the patients who have derived substantial benefit from pneumoperitoneum.

10) The induction of the hypometabolic state in the advanced, crippled pulmonary patient using radio-active iodine has been intriguing. My personal experience with this approach is too limited to be worthy of mention today. Certainly the principle of decreasing the tissue demand for oxygen in the face of an already compromised supply is quite as reasonable here as in the case of the cardiac cripple. Radio-active iodine will prove to be no panacea but may be of some benefit in a highly selected small percentage of patients with advanced pulmonary emphysema. This form of therapy is not a substitute for measures discussed previously.

SUMMARY

1. Some of the important physiolgical aberrations in severe pulmonary emphysema are reviewed. The cumulative effect of these defects frequently results in complications involving the cardio-vascular system.

2. The abuse of sedatives, narcotics and oxygen therapy is emphasized. Their relationship to the potentiality of inducing uncompensated respiratory acidosis is stressed.

3. A positive approach to therapy is presented—bronchodilators, secretory expectorants, detergents, antimicrobial therapy, pressure breathing, breathing exercises, steroid therapy, venesection, pneumoperitoneum and radio-active iodine.

RESUMEN

1. Se revisan algunas de las más importantes aberraciones fisiológicas del enfisema pulmonar. El efecto acumulativo de estos defectos, frecuentemente resultan en complicaciones cardiovasculares.

2. El abuso de sedantes, narcóticos y oxígeno terapia se destaca. Su relación con la posibilidad de producir acidosis respiratoria descompensada se recalca.

3. Se presenta un modo de ataque positivo del problema mediante el uso de bronquiodilatadores, expectorantes secretorios, detergentes, respiracién a presión positiva, ejercicios respiratorios, terapia con esteroides, oxigenoterapia, vangrías, neumoperitineo y yodo radioactivo.

RESUME

L'auteur passe en revue quelques-unes des importantes anomalies physiologiques qui surviennent dans l'emphysème pulmonaire. L'effet cumulatif de ces altérations entraine fréquemment des complications qui atteignent le système cardio-vasculaire.

L'auteur insiste sur le rôle de l'abus des sédatifs, des narcotiques et de l'oxygénothérapie. Il insiste sur le fait qu'ils peuvent être à l'origine d'une acidose respiratoire irréversible.

L'auteur présente un essai positif de traitement: par les bronchodilatateurs, les produits qui facilitent l'expectoration des sécrétions, l'exercice respiratoire, la thérapeutique par les stéroïdes, l'oxygénothérapie, la saignée, le pneumopéritoine et l'iode radioactif.

ZUSAMMENFASSUNG

1. Einige wichtige physiologische Abweichungen bei schwerem Lungenemphysem werden besprochen. Die kumulative Wirkung dieser Defekte führt häufig zu das Herz- Kreislauf-System betreffenden Komplikationen.

2. Auf den Missbrauch von Beruhigungsmitteln, Narkoticis und Sauerstoff-behandlung wird hingewiesen. Ihre Beziehung zu der Möglichkeit der Herbeiführung einer nicht kompensierten respiratorischen Acidose wird betont.

3. Eine positive Stellungnahme zur Therapie wird vorgelegt—Bronchodilatatoren, Expektorantien, Abführmittel, antimikrobielle Behandlung, Druckatmung, Atemübungen, Steroid-Behandlung, Aderlass, Pneumoperitoneum und radioaktives Jod.

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Clinical Studies of Various Forms of PAS (With Special Reference to Plasma Concentrations)* **

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Since the introduction of para-aminosalicylic acid (PAS) by Lehman in 1944, the drug has been widely used in the treatment of tuberculosis. Its chief value is the property of delaying emergence of organisms resistant to streptomycin and isoniazid. Unfortunately, however, the clinical usefulness of PAS and its sodium salt has been limited by a high incidence of gastrointestinal side-effects. In an effort to find a better tolerated and more acceptable form of medication, a clinical test of the potassium salt of PAS (KPAS) was undertaken. The potassium salt was selected because extensive previous experience in the use of para-aminobenzoic acid compounds had shown that potassium para-aminobenzoate, administered as a chilled 10 per cent solution, was generally preferred.[1, 2] That KPAS also offers a superior degree of patient tolerance and acceptance was evident early in the course of this study.[3]

The purpose of this report is to present: I. An extension of the clinical studies with KPAS to a total of 120 patients, including some observations on the administration of KPAS in tablet† and capsule† form; and, II. A comparison of the plasma PAS concentrations reached following the ingestion of several PAS compounds.

I. Clinical Studies.

Material and Methods. A. Patient Material. Since November, 1953, KPAS has been administered in therapeutic doses to 120 tuberculous patients. Pulmonary disease was present in 110, and extra-pulmonary lesions such as bone and joint involvement, adenitis, and endometritis were present in the remaining 10 patients. There were 80 males (average age 47.3 years) and 40 females (average age 36.0 years). Ninety of the patients were white and 30 Negroes. Nontuberculous complications were present in about 40 per cent of the patients: these included mild to moderate renal impairment in 10, diabetes mellitus in seven, central nervous system vascular disease in five, congestive heart failure in six, pregnancy in four, gastrointestinal disorders in eight, collagen disease in three, and isolated instances of other conditions. Throughout the study, patients with histories of intolerance

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†The Glenwood Laboratories, Teaneck, N. J., kindly furnished the bulk crystalline KPAS ("Paskalium"), tablets, and 3 gm. Envules for use in this study, while the Eli Lilly Co., Indianapolis, Indiana, contributed the capsules of KPAS ("Paskate").

and allergic reactions to PAS compounds were deliberately solicited for trial with KPAS. Only those with far-advanced renal disease were purposely not admitted to the study.

Institutions cooperating in the clinical aspects of the study included Temple University Hospital, Eagleville Sanatorium, Episcopal Hospital, and Philadelphia General Hospital (Blockley and Northern divisions). Tolerance results were evaluated not only by the authors, but also by members of the attending staffs of the participating institutions.

Twenty-three subjects received KPAS therapy as outpatients from the start, an additional 18, who began treatment in the hospital have continued to take KPAS following discharge.

B. Methods of Administration. The KPAS was obtained as pure crystalline bulk powder, as well as in tablet and capsule forms. The powder was administered as a 10 per cent aqueous solution which was kept constantly refrigerated and protected from ultra-violet light. The quantity prepared for any individual patient at one time was limited to one liter in order to prevent staleness and discoloration of the solution. The initial dosage, whether in solution, tablet or capsule form, was 2 gm. four times daily, with doses being taken immediately after meals and at bedtime. The dosage was gradually increased over a one to two week period to 3 gm. taken four times a day, or a total daily dose of 12 gm. An alternative dosage schedule of 2 gm. administered six times daily was found to be relatively inconvenient and impractical.

Patients with gastrointestinal symptoms from PAS or NaPAS medication were given a rest period of several days prior to initiating KPAS therapy. Those who manifested acquired sensitivity symptoms to PAS were "desensitized" (discussed later) only after all signs and symptoms of reaction had disappeared.

Results of Clinical Studies. Tolerance results in 120 patients treated with KPAS are given in Table I. Drug tolerance to PAS compounds is defined as the ability to ingest continuously, 12 gm. daily doses of the drug without developing gastrointestinal side-effects. Eighty-four had had previous

TABLE I
TOLERANCE RESULTS: 120 PATIENTS TREATED WITH KPAS

Drugs Used In Treatment	No. of Pts.	Intolerance to: PASA	NaPAS	KPAS
PASA KPAS	37	33		1
NaPAS KPAS	27		25	0
PASA NaPAS KPAS	20	20	20	4
KPAS	36			0
Totals	120	53 of 57	45 of 47	5 of 120
Intolerance Percentage		93%	95%	4%

therapy with either PAS or NaPAS or both; their intolerance rate to PAS was 93 per cent, to NaPAS 95 per cent, and to KPAS only 6 per cent. It should be emphasized that the high intolerance rates to PAS and NaPAS reflect the deliberate solicitation of patients with histories of intolerance to PAS compounds as mentioned previously. It is of interest that four of the five patients listed as KPAS intolerant had had similar reactions to both PAS and NaPAS administered in the past. No instances of KPAS intolerance occurred in the 36 who had had no previous PAS. The overall intolerance rate to KPAS, therefore, is 4 per cent.

Duration of KPAS therapy is summarized in Table II. Fifty patients have been on continuous medication for four months or longer, 17 for more than one year.

Tablets of KPAS were given for trial periods only to 13 subjects, all of whom had been successfully taking the solution form, six tablets (3 gm. KPAS) being substituted for each 30 cc. dose of the solution. Two of them experienced nausea, vomiting, and diarrhea. Another three complained of some vague gastric irritation, but their complaints may have been prejudiced in favor of the convenience of liquid medication. The small

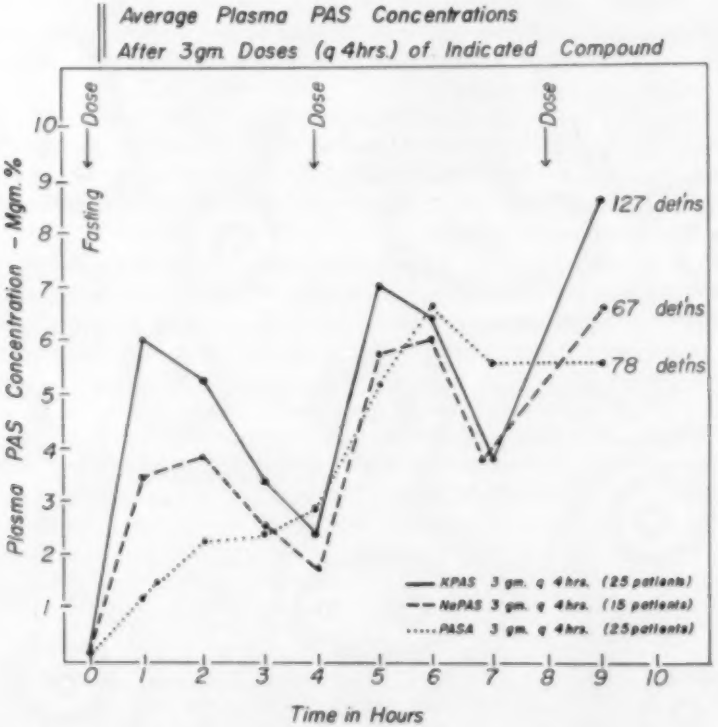

FIGURE 1: Average Plasma PAS Concentrations after 3 gm. Doses every four hours of Indicated Compounds.

TABLE II
DURATION OF KPAS THERAPY

Time in Months	Number of Cases
12 to 18	17
8 to 12	9
4 to 8	24
2 to 4	26
Less than 2	44
TOTAL	120

size and nature of this group precludes drawing any conclusions with reference to tolerance and patient acceptance of KPAS in tablet form.

Capsules of KPAS have been administered to 44, of whom 21 had had no previous KPAS, and all tolerated the capsules in 12 gm. daily doses. Of the 23 who had previously taken KPAS solution in 12 gm. daily doses, there were three who were able to tolerate only 8 gm. daily in capsule form. The intolerance rate to KPAS capsules of 7 per cent compares favorably with the 5 per cent intolerance rate of the solution form.

II. Plasma PAS Concentration Studies.

Methods and Materials. Plasma PAS concentration determinations were performed on specimens taken from 53 subjects, of whom 42 were tested with KPAS, 32 with PAS, and 22 with NaPAS. A total of 547 determinations were carried out using a modified Marshall[4] technic. The observation that plasma specimens could be stored in a frozen state for several weeks without changing PAS content greatly facilitated the technical aspects of collection and transportation of specimens. The study of plasma PAS concentrations was divided into two major parts:

Part one was an evaluation of a dosage schedule, for purposes of comparison, in which 3 gm. doses of KPAS, NaPAS and/or PAS were given at four hour intervals. Plasma specimens were collected over a nine hour period starting one hour after the first dose and ending one hour after the third dose. This study involved 297 determinations carried out on 41 subjects, KPAS being tested in 27, PAS in 23, and NaPAS in 16.

Part two was undertaken because of the observed wide variation in absorption curves in different patients when tested with the same PAS compound. Eight male subjects under treatment for tuberculosis, but without other abnormalities, were selected for testing with single 3 gm. doses of KPAS, NaPAS, and PAS given sequentially. Plasma specimens were obtained at one, two, three, and four hour intervals after the test dose. Altogether, 152 determinations were carried out in this phase of the study. KPAS, 10 per cent solution, and PAS tablets were tested in each of the eight subjects while KPAS capsules, and NaPAS tablets were each tested in six and NaPAS, 10 per cent solution, in four. PAS medication was withheld for 16 hours prior to each test, and the 3 gm. dose of drug was administered immediately following the subject's usual breakfast.

Results of Plasma PAS Concentration Studies. Part one. PAS compounds administered in 3 gm. doses, at four hour intervals. The average plasma PAS concentrations reached following the administration of KPAS, NaPAS, and PAS are shown in Fig. 1. Calculation of the average concentrations resulting from this dosage over the nine hour period gives values of 5.5 mg. per cent for KPAS, 4.0 mg. per cent for NaPAS, and 3.6 mg. per cent for PAS. (Table III.) KPAS, therefore, produced plasma concentrations which were approximately one-third higher than NaPAS, and one-half again higher than those obtained with PAS.

Part two. Levels achieved with single 3 gm. doses of PAS compounds administered to the same eight subjects. The average plasma PAS concentrations obtained in this group after the administration of KPAS, NaPAS, and PAS are shown in Figure 2.

Table IV gives the four hour average plasma PAS concentration for each compound tested in this group. Although there are some individual variations, the values after KPAS were consistently higher than those following NaPAS or PAS.

In Figures 3, 4, and 5 are shown the results in individual subjects and demonstrate the findings with each of the six drug forms tested.

The average plasma PAS levels obtained in five subjects who were given KPAS in solution, tablet, and capsule form are compared in Fig. 6. As can be seen, slightly higher plasma concentrations were produced by the capsules than the solution form, and the latter in turn yielded some-

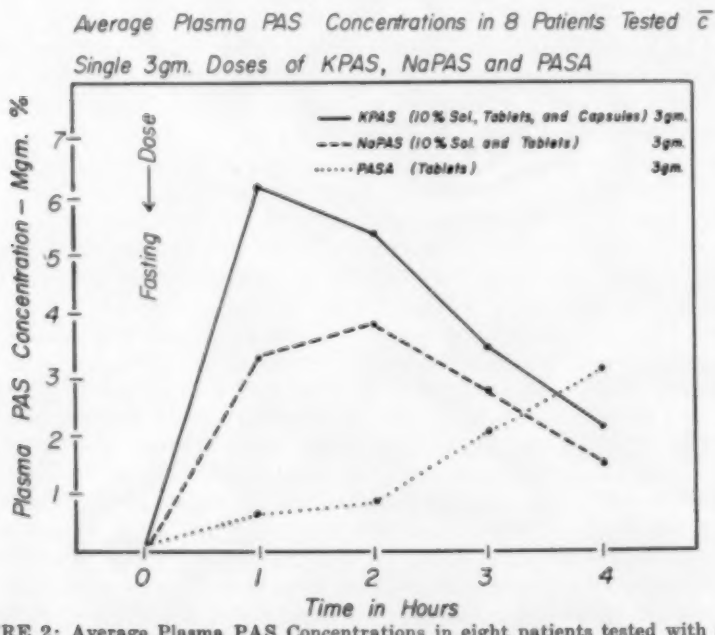

FIGURE 2: Average Plasma PAS Concentrations in eight patients tested with single 3 gm. Doses of KPAS, NaPAS, and PAS.

TABLE III
9-HR. AVG. PLASMA PAS CONCENTRATIONS
DOSAGE SCHEDULE
3 GM. q4H OF INDICATED COMPOUNDS

297 Determinations	
KPAS	5.5 mg.% (27 pts.)
NaPAS	4.0 mg.% (16 pts.)
PASA	3.6 mg.% (23 pts.)

what higher values than did the tablets. However, these differences may not be significant.

Preliminary studies of PAS concentrations in pleural, peritoneal, and cerebrospinal fluids have yielded values that were about one-half those present in plasma specimens taken simultaneously.

Discussion. Continued clinical experience has confirmed the earlier opinion[3] that potassium para-aminosalicylate (KPAS) offers a high degree of patient tolerance and acceptance. Indeed, 115 (96 per cent) of 120 patients have tolerated, without difficulty, 12 gm. daily doses of KPAS. This finding is even more striking when it is recalled that 78 (65 per cent) of the group had shown intolerance to previous therapy with PAS or NaPAS. Furthermore, many of these patients have continued to receive KPAS over extended periods. This is an important criterion of therapeutic value since the duration of antimicrobial therapy in tuberculosis is currently measured in terms of months and even years. In this connection, it may be noted from the data given in Table II that 17 patients have taken 12

TABLE IV
4-HOUR AVERAGE PLASMA PAS CONCENTRATIONS (MG%)
AFTER 3-GRAM DOSES OF INDICATED COMPOUNDS

	KPAS			NaPAS		PASA
Pt.	Capsules	Sol. 10%	Tablets	Sol. 10%	Tablets	Tablets
J. A.	4.6	4.1	3.3	2.5	3.0	1.2
R. H.	5.1	3.5	4.0	4.0	1.1	1.3
R. W.	3.5	3.2	2.7		2.2	0.8
A. G.	4.4	3.2	3.7	2.6		3.4
H. S.	4.8	6.2	5.2		4.4	0.8
E. K.	5.0	5.0		3.0		1.4
J. M.		3.2	3.5		2.8	3.2
J. K.		6.9			4.1	1.7
Avg.	4.6	4.4	3.7	3.0	2.9	1.7
		4.3			3.0	1.7

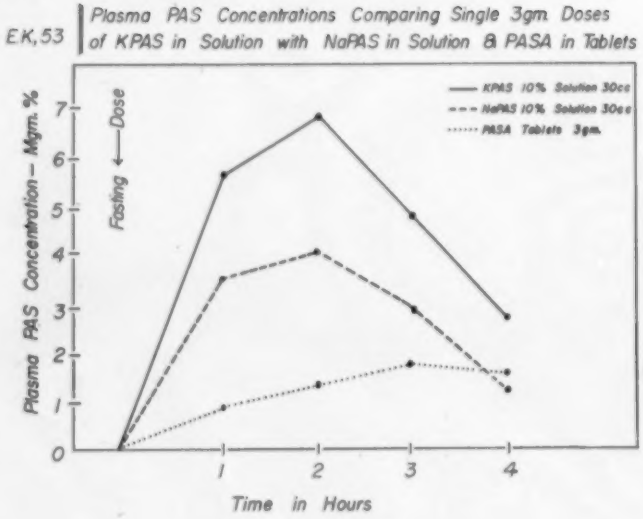

FIGURE 3

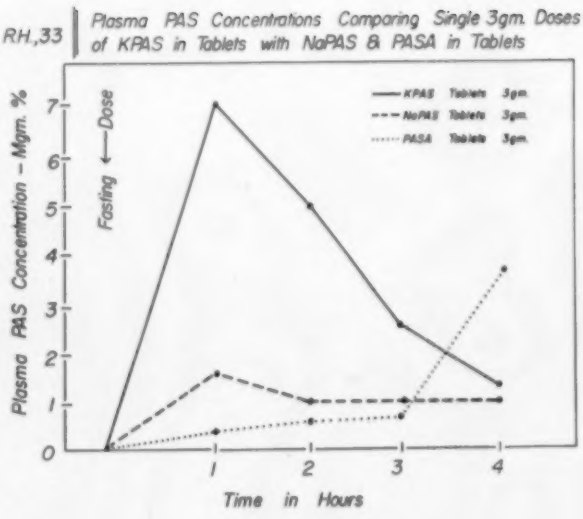

FIGURE 4

Figure 3: Plasma PAS Concentrations Comparing Single 3 gm. Doses of KPAS in Solution with NaPAS in Solution and PAS in Tablets; Patient E. K., aged 53 years.—*Figure 4:* Plasma Concentrations Comparing Single 3 gm. Doses of KPAS in Tablets with NaPAS and PAS in Tablets; Patient R. H. aged 33 years.

gm. daily doses of KPAS for periods ranging from 12 to 17 months. Nine of these had been unable to tolerate prior therapy with PAS, while eight had received no previous PAS. Altogether, 76 subjects have been on KPAS therapy for two months or longer.

KPAS was administered to the majority of these patients as chilled, 10 per cent aqueous solution. The success and economy of this form of therapy have more than compensated for the minor inconveniences coincident to solution medication. Capsules and tablets of KPAS compare favorably with respect to plasma concentrations, and in most instances appear equally tolerated. There were a few who expressed preference for a specific form of KPAS medication, so that individualization of treatment is necessary. The packaging of KPAS powder in individual 3 gm. doses (Envules) has proved to be practical for those who work and who prefer the solution form. Others have found the capsules or tablets equally convenient.

Plasma PAS concentration studies indicate that KPAS is promptly absorbed and productive of effective blood levels, regardless of the dosage form employed (Fig. 6). Furthermore, the average plasma concentrations reached following administration of KPAS were uniformly superior to those found after PAS or NaPAS (Figs. 1 through 5, Tables III and IV). In view of possible differences in absorption of PAS compounds by different subjects, plasma concentrations were determined in each of eight patients after single 3 gm. doses of KPAS, NaPAS, and PAS, respectively. Again, KPAS yielded markedly superior plasma PAS concentrations (See Fig. 2 and Table IV). The basis for this superiority of KPAS-induced plasma concentrations is not clear at this time. Possibly the extremely high solubility of KPAS may be a factor. However, when NaPAS was also administered in 10 per cent solution, the plasma PAS levels did not approach those obtained with KPAS in 10 per cent solution. In fact, the values produced by NaPAS in solution were comparable to those following tablets of NaPAS. Since tablets and capsules, as well as the 10 per cent solution, of KPAS all yielded plasma concentrations higher than did NaPAS and PAS, it would appear that the difference is an inherent property of the potassium preparation. An investigation of comparative absorption curves of sodium and potassium salts of other organic compounds is now underway in an effort to elucidate this finding.

No toxic effects have been detected from KPAS in this group. Conventional blood, urine, and liver function tests in representative cases have shown no changes incident to treatment with KPAS. Serum potassium concentrations have remained within normal limits following the administration of 3 gm. doses of KPAS.

One patient did manifest an acquired sensitivity reaction while receiving KPAS. The drug was discontinued, and "desensitization" was subsequently carried out and the patient has since been able to take 12 gm. daily without any difficulty. Five additional cases who had similar reactions to other PAS compounds were also "desensitized" and have since been on full therapeutic doses of KPAS. "Desensitization" was accomplished with the 10 per cent solution of KPAS, beginning with 1 drop,

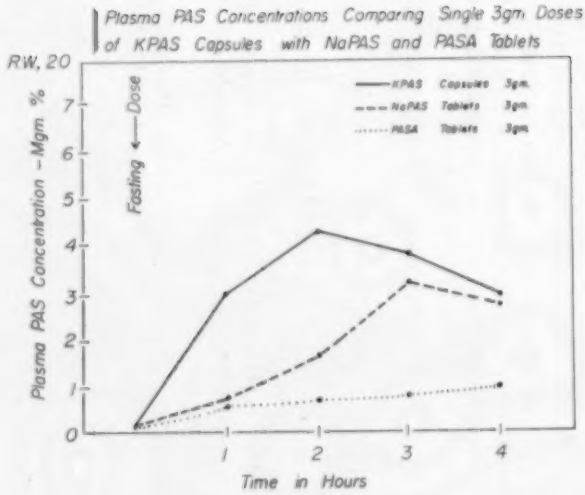

FIGURE 5

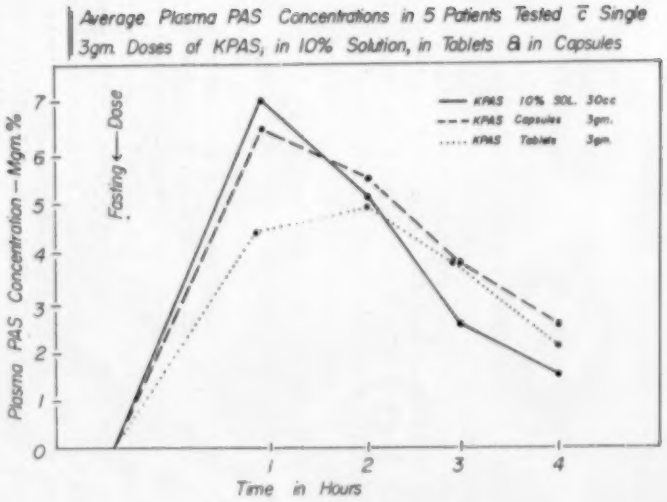

FIGURE 6

Figure 5: **Plasma PAS Concentrations Comparing Single 3 gm. Doses of KPAS Capsules with NaPAS and PAS Tablets; Patient R. W. aged 20 years.—*Figure 6:* Average Plasma PAS Concentrations in five Patients Tested with Single 3 gm. Doses of KPAS; in 10 per cent Solution, in Tablets, and in Capsules.**

given four times the first day, and gradually increasing the dose for succeeding days until the desired 12 gm. (120 cc.) total was reached.

An additional advantage of potassium salt is its usefulness in the treatment of those for whom sodium restriction is necessary because of congestive heart failure, pregnancy, or steroid hormone therapy. For example, one patient with systemic lupus erythematosus, and another with Henoch-Schoenlein purpura, required cortisone. Both were able to remain on an anti-tuberculosis regimen without interruption. In fact, KPAS also supplied an adequate source of potassium ions for support of the steroid program.

Finally, it appears that the *minimum* duration of combined antimicrobial therapy in tuberculosis is becoming longer and longer. It has changed from six weeks, to six months, and to a year. No one yet knows the ideal *maximum* duration of drug treatment in certain long-term cases. For this reason, it is believed that the observations reported herein are pertinent: the potassium salt has been found to be the least objectionable form of PAS; at the same time, it is most rapidly absorbed and produces the highest plasma PAS concentrations.

SUMMARY

Potassium para-aminosalicylate (KPAS) was administered to 120 patients with tuberculosis.

One hundred fifteen (96 per cent) tolerated 12 gm. daily doses of KPAS without difficulty. There were no evidences of potassium toxicity.

Plasma PAS concentration studies revealed that KPAS is more rapidly absorbed and yields significantly higher values than either PAS or NaPAS.

KPAS is ideally suited for use in patients with congestive heart failure, pregnancy, or other situations in which use of the sodium salt is precluded.

The 10 per cent solution of KPAS was used for "desensitizations" of those who had acquired sensitivity reactions to PAS compounds.

It is concluded that KPAS is superior to other forms of PAS.

Acknowledgment: The authors wish to express their appreciation to Miss Virginia F. Colville, Miss Betty Kane, and Miss Roberta Stauffenberg for technical assistance throughout the course of this study.

RESUMEN

Se administró paraminosalicilato de potasio (KPAS) a 120 enfermos de tuberculosis.

Ciento quince (96 por ciento) toleraron 12 gramos diarios de KPAS sin dificultad. No hubo evidencias de toxicidad potásica.

Los estudios sobre la concentración de PAS en el plasma revelaron que el KPAS es absorbido más rápidamente, proporciona tenores significantes más elevados que el PAS o el NaPAS.

KPAS es adecuado idealmente para el uso en enfermos con insuficiencia cardiaca congestiva, embarazo, o en otras condiciones que no permiten el uso de la sal sódica.

Se usó la solución al 10 por ciento de KPAS para "desensibilizar" aquéllos que han adquirido sensibilidad reaccional a los compuestos de PAS. Se concluye que el KPAS es superior a las otras formas de PAS.

RESUME

Du para-aminosalicylate de potassium (KPAS) fut administré chez 120 malades atteints de tuberculose.

115 (96%) ont toléré des doses quotidiennes de 12 gr. de KPAS sans difficulté. On ne constata pas d'accidents toxiques dus au potassium.

Les études sur la concentration de PAS dans le plasma révélèrent que le KPAS est plus rapidement absorbé et donne des indices nettement plus élevés que le PAS ou le PAS sodique.

Le KPAS peut trouver son utilisation idéale chez les malades atteints de défaillance cardiaque congestive, chez les femmes enceintes, ou toutes autres conditions dans lesquelles l'emploi du sodium doit être cessé.

La solution à 10% de KPAS est utilisée pour la désensibilisation de ceux qui ont acquis des réactions de sensibilité aux composés du PAS.

L'auteur conclut que le KPAS est supérieur à toutes les autres formes de PAS.

ZUSAMMENFASSUNG

Kalium Para-Aminosalicylsäure (KPAS wurde an 120 Patienten mit Tuberkulose gegeben.

115 (96%) vertrugen 12 Gramm täglich KPAS ohne Schwierigkeiten. Es fanden sich keine Anzeichen einer Kalium-Toxizität.

Untersuchungen über PAS-Konzentration im Plasma ergaben, dass KPAS rascher absorbiert wird und beträhtlich höhere Werte ergibt, sowohl als PAS als auch als NaPAS.

KPAS eignet sich in idealer Weise zum Gebrauch bei atienten mit Versagen des Herzens durch Stauung, bei Schwangerschaft oder unter anderen Umständen, in denen die Benutzung des Natrium-Salzes ausgeschlossen ist.

Die 10%ige Lösung von KPAS wurde zur "Desensibilisierung" in den Fällen benutzt, die sich Überempfindlichkeitsreaktionen auf PAS-Verbindungen zugezogen hatten. Es wird gefolgert, dass das KPAS anderen PAS-Formen überlegen ist.

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Chlorpromazine* in the Control of Side Effects of Para-Aminosalicylic Acid Administration

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Courses of antituberculous chemotherapy are more prolonged than ever, and the problem of the unpleasant side effects of the administration of para-aminosalicylic acid (PAS) harasses both patient and physician for longer periods of time. Clinicians who manage tuberculosis are quite familiar with the difficulties entailed in keeping an appreciable number of their patients on an uninterrupted, prolonged course of para-aminosalicylic acid. In my experience, at least 25 per cent of patients receiving this antituberculous drug develop anorexia, epigastric distress, nausea, vomiting, abdominal cramps, or diarrhea. Quite an appreciable number discontinue the medication on their own or have it discontinued by the physician because of these symptoms. Many others who continue the drug despite these unpleasant symptoms, have the extra burden of side effects added to the already heavy burden of tuberculosis, with its physical, social, economic and emotional difficulties.

The physician is faced with the problem of finding either a form of the drug that will be tolerated or an adjuvant that will help control the unpleasant symptoms. Among the variations of the drug used are buffered tablets, granules, coated tablets, and salts of the acid. Recently, potassium para-aminosalicylate has been recommended for use in place of other para-aminosalicylic acid preparations, as carrying a high degree of patient tolerance and acceptance.[1] Many different medicaments have been employed as adjuvants with varied degrees of success in an attempt to control the unpleasant side effects. Among them are the antacids, tincture of belladonna, other antispasmodics, camphorated tincture of opium, and dramamine.®[2] The effectiveness of chlorpromazine in the control of drug induced nausea and vomiting is well known.[3, 4, 5] It is the purpose of this paper to present the results of the use of this versatile drug in the control of side-effects of oral administration of para-aminosalicylic acid in the treatment of pulmonary tuberculosis.

Material

A total of 91 patients (87 males and four females) who experienced side effects attributable to para-aminosalicylic acid during courses of chemotherapy, and were treated with chlorpromazine are included in this study. They ranged from 21 to 63 years of age, with an average of 39. Both hospitalized and ambulatory patients are included. Those hospitalized were

*Kindly supplied as "Thorazine" by Smith, Kline & French Laboratories, Philadelphia, Pa.

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treated by the staff of two private pulmonary disease hospitals. The ambulatory cases were treated by the Veterans Administration Regional Office in San Juan, Puerto Rico and by private physicians. All included in this report were receiving buffered PAS tablets orally in doses of 12 Gm. daily. All complained of symptoms attributable to PAS. These symptoms are listed in Table I in descending order of occurrence. Many had more than one of these complaints. Patients who received medications other than antituberculous chemotherapy and chlorpromazine during the period of this study are not included in this report.

TABLE I
SIDE EFFECTS ATTRIBUTABLE TO PARA-AMINOSALICYLIC ACID

Epigastric burning	56
Anorexia	48
Diarrhea	42
Nausea	32
Abdominal cramps	20
Pyrosis	10
Vomiting	6
Constipation	4
Epigastric pain	2
Epigastric fullness	2
Flatulence	2
Itching, generalized	1

Method

When a patient receiving para-aminosalicylic acid developed symptoms of intolerance, the drug was discontinued for three to seven days. If symptoms improved or disappeared, PAS in full dose was resumed. If symptoms recurred upon resuming PAS, chlorpromazine was given orally in tablet form in doses of 25 mg. three times daily .This "PAS withdrawal" was carried out in 58 of the 91 patients. In the remaining 33, chlorpromazine was administered after the patient had had symptoms of PAS intolerance for several days, without going through the "PAS withdrawal period." In the beginning, both drugs were given simultaneously, but later, chlorpromazine was administered about one hour before each dose of para-aminosalicylic acid. The dose of chlorpromazine was adjusted according to the patient's clinical picture, A placebo tablet, identical in appearance to the commercially available "Thorazine" tablets, was used in carrying out multiple substitutions without the patients' knowledge. These substitutions were carried out in 67 of the 91 patients. Administration of the drug was continued for periods ranging from two weeks to four months. The placebo was used to determine whether discontinuation of chlorpromazine would be accompanied by a return of symptoms of PAS intolerance.

Results

The effective dose was found to be 25 mg. three times daily in 87 cases, 50 mg. three times daily in one, and 10 mg. three times daily in the remaining three. There was complete disappearance of symptoms of PAS intolerance in 64 (70.3 per cent), partial relief of symptoms in three (3.3 per cent) and no relief in the remaining 24 (26.4 per cent). In this latter group, para-aminosalicylic acid had to be discontinued either by the physician or by the patient himself. The one who complained of generalized itching experienced complete relief. Chlorpromazine gave either partial or complete relief of symptoms of PAS intolerance in one to six days. The majority of cases reported complete relief within three days.

Side Effects of Chlorpromazine

The only side effects attributable to chlorpromazine were drowsiness (18 cases), dizziness on standing (two cases, one of them hypertensive), vague feeling of dizziness or "light-headedness" (three cases), and terrifying nightmares (two cases). If a patient complained of drowsiness, the dose of the drug was either reduced or continued at the same level and it was explained that within a few days he would be able to tolerate the drug. In four to five days, drowsiness disappeared. In those cases in which the dosage had been reduced and it was felt that the higher dose was needed, the latter was resumed without recurrence of drowsiness. In only one (female) did the drug have to be discontinued because of sleepiness that occurred even on 10 mg. once daily. The two who complained of dizziness on standing were controlled by reducing the dose of chlorpromazine to 25 mg. twice daily. The "light-headedness" of which three complained disappeared spontaneously without change in drug dosage. In the two who had nightmares chlorpromazine was discontinued entirely. One of them had nightmares even after the drug had been discontinued for one week and the placebo administered instead. He refused further medication.

Discussion

It is well known that many patients who develop symptoms which may be described as side effects of para-aminosalicylic acid are able to tolerate the drug after having been reassured by their physicians. This applies particularly to gastrointestinal symptoms. The reassurance may aid in relieving the tensions and anxieties which are so common in the tuberculous. Moyer and others[5] reported good results with the use of chlorpromazine in ambulatory psychiatric cases who had tension and anxiety states. Winkelman[6] also reported good response to chlorpromazine in these cases. Without doubt, the mood ameliorating properties of chlorpromazine account in great measure for the relief experienced by many patients in this study. In quite a few instances they reported a sense of well-being. This particular property of chlorpromazine may well have accounted for the relief of itching in those who had this complaint.

Anorexia was a particularly troublesome complaint in this group. Patients'

concern over the fact that they were not eating made matters worse. There was rapid increase in appetite once chlorpromazine was begun. Moyer and others[5] have reported striking stimulation of appetite by chlorpromazine to such an extent that this was utilized as a method of increasing weight. Diarrhea due to PAS was a common complaint among our patients, but subsided rapidly with chlorpromazine. Constipation is the most frequent gastrointestinal disturbance produced by this latter drug, and has been listed as a sign of the effect of the drug on the autonomic nervous system. In patients with diarrhea, this effect is of definite benefit. Paradoxically, of four patients who complained of constipation apparently due to PAS, three were relieved upon administration of chlorpromazine. This may have its explanation in relief of tension and anxiety. Nausea and vomiting were relieved promptly, as were the other gastrointestinal manifestations of PAS intolerance listed. Regardless of the mechanisms involved, the impressive fact is the prompt relief of unpleasant symptoms.

Chlorpromazine was not administered parenterally. Many were receiving streptomycin intramuscularly two or more times a week, and it was not considered either wise or necessary to add more injections to their treatment. The oral route of administration proved effective.

Placebo tablets were used for multiple substitutions to eliminate as completely as possible the psychogenic effect of this extra added medication as an important factor in the results obtained. In many instances we were able to reproduce or relieve at will the manifestations of intolerance to para-aminosalicylic acid. The placebo was used also to determine whether the patient would continue to tolerate PAS without adjuvants thereafter.

In the majority of cases, it was necessary to continue chlorpromazine for two to six weeks. Others had to continue up to four months. In the doses used, there were practically no side effects of chlorpromazine that were not easily controlled by reducing dosage temporarily. In most cases, once tolerance to the drug was developed, we were able to resume its administration at a higher dosage. Judging from this study it would seem advisable to start on 25 mg. of chlorpromazine orally when symptoms of PAS intolerance develop. This amount is high enough to bring about rapid relief of symptoms and low enough to cause little difficulty. The patient should be informed of the possibility of drowsiness and assured that this will disappear once he develops tolerance. Once an aversion to PAS develops, it may be difficult to convince him to take it regularly over long periods of time. This is why the slightly high initial dose of chlorpromazine is recommended. Thereafter the dose has to be adjusted according to the clinical picture.

SUMMARY

1. A group of 91 patients who had developed unpleasant side effects (mostly gastrointestinal) attributable to para-aminosalicylic acid (PAS) during courses of antituberculous chemotherapy, were treated with chlorpromazine orally. This latter drug was administered in doses of 25 mg. three times a day for two to six weeks in most cases.

2. There was complete relief of symptoms in 70.3 per cent of patients, partial relief in 3.3 per cent, and no relief in 26.4 per cent. Subsidence of symptoms was brought about in one to six days.

3. In the doses used, side effects of chlorpromazine were few and not troublesome. Drowsiness occurred in 19.7 per cent, dizziness on standing in 2.2 per cent, vague feeling of dizziness or "light-headedness" in 3.3 per cent, and terrifying nightmares in 2.2 per cent. In all cases, except two with nightmares, symptoms were controlled by reducing the dosage of chlorpromazine.

4. Oral administration of chlorpromazine is an effective method in the control of most unpleasant side effects of para-aminosalicylic acid.

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RESUMEN

1. Se trataron con cloropromazina (Largactil) los efectos desagradables la mayoría gastrointestinales, atribuibles al PAS en 91 enfermos de tuberculosis, dándose la cloropromazina por vía oral. Esta droga fué usada a la dosis de 25 mg. tres veces al día por seis semanas en la mayoría de los casos.

2. Hubo alivio completo de los síntomas en 70.3 por ciento de los enfermos; alivio parcial en 3.3 por ciento y ningún alivio en 26.4 por ciento. El alivio de los síntomas se obtuvo en uno a seis días aproximadamente.

3. A las dosis usadas los efectos de la cloropromazina fueron pocos y no molestos. Somnolencia 19.7 por ciento, mareo al estar de pie en 2.2 por ciento, vaga sensación de mareo o de ligereza de cabeza en 3.3 por ciento y pesadillas terroríficas en 2.2 por ciento. En todos los casos excepto en dos con pesadillas, los síntomas se dominaron disminuyendo la dosis de cloropromazina.

4. La administración oral de cloropromazina es un método efectivo para el control de los desagradables efectos colaterales del PAS.

RESUME

1. Un groupe de 91 malades qui furent atteints de manifestations désagréables (pour la plupart gastro-intestinales) imputables à l'acide para-amino-salicylique (PAS) au cours de la chimiothérapie antituberculeuse, furent traités par la "chlorpromazine" par voie buccale. Cette dernière drogue fut administrée dans la plupart des cas aux doses de 25 mmgr. trois fois par jour pendant deux à six semaines.

2. Il y eut un soulagement complet des symptômes chez 70,3% des malades, un soulagement partiel chez 3,3% et aucun soulagement chez 26,4% d'entre eux. La régression des symptômes se fit en un à six jours.

3. Dans les doses utilisées, les effets secondaires de la "chlorpromazine" furent rares et non pénibles. Une somnolence survint chez 19,7%, des vertiges à la station debout chez 2,2%, une vague impression de vertige ou de "tête légère" chez 3,3% et des cauchemars chez 2,2%. Dans

tous les cas, sauf deux qui manifestèrent des cauchemars, les symptômes furent jugulés en réduisant la dose de chlorpromazine.

4. L'administration de chlorpromazine par voie buccale est une méthode efficace pour juguler les effets secondaires les plus désagréables de l'acide para-amino-salicylique.

ZUSAMMENFASSUNG

1. Eine Gruppe von 91 Patienten, bei denen unangenehme Nebenwirkungen (meist gastrointestinal) im Verlauf einer antituberkulösen Chemo-Therapie aufgetreten waren, die der PAS zuzuschreiben waren, wurde oral mit Chlorpromazin behandelt. Dies letztere Mittel wurde verabfolgt in Dosen von 25 mg. 3 täglich, während 2-6 Wochen in den meisten Fällen.

2. Es ergab sich eine vollständige Beseitigung der Symptome in 70,3% der Kranken, eine teilweise Beseitigung in 3,3%, und keine Beseitigung in 26,4%. Zu einem Nachlassen der Symptome kam es innerhalb von 1-6 Tagen.

3. In der gebrauchten Dosierung gab es nur wenige und keine lästigen Nebenwirkungen. vom Chlorpromazin. Schläfrigkeit trat in 19,7% auf, Schwindel beim Stehen in 2,2%, unbestimmtes Schwindelgefühl dore "Benommenheit" in 3,3%, und schweres Alpdrücken in 2,2%. In Allen Fällen, abgesehen von 2 mit Alpdrücken liessen sich die Symptome bekämpfen durch Verringerung des Dosis des Chlorpromazins.

4. Orale Verwendung von Chlorpromazin ist eine wirksame Methode bei der Bekömpfung von unangenehmen Nebenerscheinungen von PAS.

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The Achilles Heel of Tuberculosis Control

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I am sure you all remember the story of Achilles, the great hero of the Homeric Legend. His mother, wanting to make him immortal, dunked him by the heels in the River Styx. Unfortunately, goddess though she was, she made a mistake. To be sure that the water to confer life everlasting reached every part of the baby's body, she should have reversed her field and dunked him by the ears after dunking him by the heels. The unbathed heels of Achilles remained vulnerable and cost him his life! Hence, the saying to this day "The vulnerable heel of Achilles."

What is the Achilles heel or the vulnerable spot of tuberculous disease? The weak spot of our enemy, tuberculous disease, is its curability in its early stage. Its strong point is its capacity for multiplication by virtue of its contagiousness. Ignorance and delay in diagnosis inevitably result in one person with open tuberculosis infecting one or more other persons and these each infect one or more other persons and so on *ad infinitum*.

It is as simple as guinea pigs and dandelions! This multiplication business has got to stop! Find the early case, cure it with chemotherapy, prevent it from becoming a spreader of disease.

There's nothing new in this. We have been so busy on the one hand with our humanitarian efforts to relieve suffering that we have failed on the other hand to prevent suffering. It's true that we formerly lacked the powerful chemotherapeutic agents we now have but for years we have had the most important diagnostic tool available for any infectious disease, the *tuberculin test*. The weak spot of tuberculosis control is the incontrovertible fact that about six weeks after a human being is infected, we can by a simple and a highly reliable test tell that he *has* been infected.

The significance of the tuberculin test may be summarized thus: A person not infected with the tubercle bacillus is not sensitive to tuberculin! A person not infected cannot be made sensitive to tuberculin just by its repeated use. When the test is positive, that person harbors a tuberculous focus somewhere in the body. A weakly positive test does not disprove clinically active tuberculosis! Likewise, a strong test does not prove the presence of clinically active disease! Therefore, the *single* tuberculin test has its limitations. When positive it can tell only that infection has taken place. It cannot tell *where* that infection is in the body; it cannot tell *how bad* it is; it cannot tell *where* it was acquired, or *when* it was acquired. But, perhaps I am being unfair to the test. There is nothing really wrong with it. The Achilles heel is on the foot of the doctor who does not *do* the test. To tell the truth the doctor has two heels and he is vulnerable in both

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of them. He is vulnerable because he does not use this test routinely on all his patients and he is again vulnerable because he does not repeat it when he should. Repetition of this test in timely fashion would furnish two vitally important facts. We would learn *when* the infection took place, perhaps *where* the infection took place and even the source of the infection. This information is essential to the protection not only of the person being tested but to all those who already have been infected by the same source, and all those who *might* be infected if this source is not controlled.

Prompt recognition of the time of infection, which can be done only by use of the repeated tuberculin test, gives us a chance to treat this disease at the earliest possible moment. What then? We must stop tuberculosis before it goes to seed and the seed are spread all over the place. For *this* we are dependent upon the x-ray film and chemotherapy. Here, are the three great weapons against tuberculosis the tuberculin test, the x-ray film and chemotherapy. Day by day, almost hour by hour, we are gathering experience in the use of these weapons. I trust I may be forgiven in the next world, if not in this, for waxing impatient in our campaign to secure widespread use of the tuberculin test and x-ray films of *all* admissions to *all* general hospitals *on admission, regardless of diagnosis.*

Do we tuberculin test and make chest x-ray films of all of our school teachers? De we test and x-ray film contacts of newly diagnosed patients with tuberculosis, in the home, in the business office, in the hospital, in industry? Do we periodically test and x-ray film all nurses, medical students, interns as well as patients? Do we test and x-ray film all new patients coming to our (doctor's) offices and periodically check all "inactives," all formerly "actives" and all "suspects"? Dc we check one intimately associated in any way with our penal institutions, with our mental institutions, with the various institutions and organizations for the care of the aged and the homeless? Do we test and x-ray film every man entering military service, army, navy, marines, air force? Do we do these things regularly, routinely, repeatedly? It is my understanding that every man in the British Navy has an x-ray film annually and that shortly every man in the British armed forces will be x-rayed annually.

Now, as to therapy! We have these wonderful drugs, perhaps we will get others more safe and more effective. Wisely used, present drugs will do a good job for us. The recent converter of the tuberculin test from negative to positive has been recently infected with the tubercle bacillus. He has tuberculous infection. What are his chances of developing tuberculous disease? I can give you no precise figures and I will cheerfully grant that on the average the risk is not great, but you will have to admit that the future is not predictable with certainty. We x-ray film these recent converters. No lesion may be demonstrated but we know radiology has its limitations and a lesion, a primary complex must be present in the vast majority of circumstances.

If this primary complex is revealed by the x-ray film, I am more fearful of the future than if it is not. I also am more fearful if this recent converter is a contact in a tuberculous family, if it is an infant, or a young

child, an adolescent girl, a young pregnant woman, a trained nurse, a medical student, an intern or resident, a diabetic, a silicotic, a psychotic, a homeless old man, to mention a few of the most exposed and vulnerable. I will concede that the menace of a primary focus is not as great as a later developing lesion, the so-called "reinfect" infiltrate. Nevertheless, ample evidence supports the opinion that much clinically significant disease follows rapidly, within a year or two if not within months, on top of primary infection. This applies to adults as well as to infants and young children. At this time, despite the fact that we have very effective chemotherapeutic agents which can be administered by mouth without undue fear of toxicity, I cannot recommend the wholesale treatment of all recent converters without x-ray film demonstrable pulmonary lesions. I do urge chemotherapy for those persons that fall within the groups mentioned in the early part of this paragraph, in other words, recent converters among highly exposed persons. I also confess that I would be in a quandary when *not* to treat a recent converter without demonstrable lesion! It is devoutly hoped that present studies of major proportion will resolve this important matter.

Opposition to the treatment of recent converters is important and powerful. In view of the fact that chemotherapy is available, not burdensome economically, or difficult of administration, not dangerously toxic *in experienced hands*, admittedly most effective in early lesions, it seems to me a heavy burden of responsibility rests on those who say *don't use it* under *these conditions*, rather than on those who say, you *should use it*. If advanced tuberculosis will regress under chemotherapy, why will, a *little* tuberculosis not also regress? The answer I usually get to this question is evasive. It is: Chemotherapy for this situation is unnecessary. The vast majority of these recent converters will get well without chemotherapy or will never get sick. Unfortunately, *some will shortly* come down with active disease and others will surely develop clinical disease in remote years. No one can say with assurance which will escape and which will not. Minimal tuberculosis of the lungs today is being treated everywhere with chemotherapy. Just how minimal does pulmonary tuberculosis have to be before one would not treat it?

Treatment of a few early cases of tuberculosis has brought about reversion of the tuberculin test. This fact should be taken as an indication of the amenability of the vulnerability of this early disease to chemotherapy. Have no anxiety about the susceptibility of this person with reversion of the tuberculin test! In my opinion he will still retain his former native resistance and also some measure of his acquired resistance. He is safer than if he had never been infected and infinitely safer than if he had not had chemotherapy and so been rid of his infection.

It is to be expected that the incidence of tuberculous infection will continue however slowly to fall, and therefore, the number of recent converters, young and old, will decrease. R. J. Anderson estimates the decline in newly reported cases to be only 3 per cent per year! Whether I am right or not about this and the importance of treating recent converters, it is still of supreme importance to convince the medical profession of the value of the

repeated tuberculin test and the periodic x-ray film of the chest. Please note carefully my emphasis on the words *repeated* and *periodic!* It is not enough to urge the use of tuberculin test and the x-ray film. We must always couple the words *repeated tuberculin test* and *periodic x-ray film.* Ordinary methods of case finding turn up too high a percentage of moderately or far advanced cases, 78 per cent, according to Anderson.

It is necessary to convince doctors to do three things and the people, children and their parents, to submit to them. The program of the American School Health Association is ideally designed to contribute powerfully to this campaign of education.

In conclusion, what I have said can be summed up in one short sentence: *Don't let your dandelions go to seed!*

If this appears cryptic, I will add, cure your tuberculosis before it becomes an open, advanced, communicable disease and spreads the seeds of disease to relatives, friends and neighbors.

SUMMARY

The Achilles Heel of Tuberculous Disease, its vulnerable spot is its curability in its early stages, its strong point is its capacity for multiplication by virtue of its contagiousness in its advanced stages. One person with active disease infects others and each of these infects others and so on ad infinitum. The old term for it would be "geometrical progression," the modern term, "chain reaction." The person with advanced disease spits more tubercle bacilli and is a more potent spreader of disease than the person with minimal disease who spits few or no tubercle bacilli.

To control tuberculosis, therefore, we must discover and treat the early case, and prevent it from becoming the advanced case, the chief spreader of disease! The combined use of the tuberculin test, the x-ray film of the chest and chemotherapy will enormously reduce the spread of the disease. The tuberculin test wisely repeated will tell not only that infection has occurred but will tell *when* it occurred and frequently *where* it occurred and even the *source* of that infection. Likewise, the x-ray film of the chest must be repeated at appropriate intervals, especially at certain ages and with highly exposed groups of persons, on all positive reactors whether recent converters or not!

Conviction is settled that minimal active pulmonary tuberculosis should be treated with chemotherapy. Just how minimal does tuberculosis have to be before one would not treat it with chemotherapy? The next few years will answer this question. At present, it seems wise to treat with chemotherapy recent converters in highly exposed groups and recent converters at the most vulnerable ages.

RESUMEN

El tendón de Aquiles es la tuberculosis, su punto vulnerable, radica en la etapa temprana de la enfermedad. Su punto fuerte en cambio es su capacidad de multiplicación en virtud de su contagiosidad en las etapas avanzadas.

Una persona con la enfermedad activa infecta a otras y cada una de éstas a su vez, a otras y así hasta el infinito.

La antigua expresión para esto sería "progresión geométrica" la moderna sería "reacción en cadena." La persona con tuberculosis avanza da expectora más bacilos y es un diseminador más potente de la enfermedad que la persona con enfermedad mínima que expectora pocos o ningúnbacilo.

Para controlar la tuberculosis por tanto, debemos descubrir y tratar el caso temprano y evitar que se convierta en avanzado que es el diseminador principal de la enfermedad.

El uso combinado de la reacción tuberculínica, la radiografía del tórax y la quimioterapia reducirá enormemente la difusión de la enfermedad. La prueba tuberculínica repetida como es debido dirá no sólo que la infección ha ocurrido sino que expresará *cuándo* ha ocurrido y frecuentemente *dónde* ha ocurrido y aún señalará la *fuente* de esa infección.

Asimismo, la película de rayos X del tórax, debe repetirse a intervalos adecuados especialmente a ciertas edades en los grupos altamente expuestos, en todos los reactores positivos a sean recien vira dos o no!

Se ha establecido ya la convicción de que los casos de tuberculosis mínima deben tratarse con quimioterapia. Qué tan mínima exactamente tiene que ser la tuberculosis para que no sea tratada con quimioterapia? Los próximos pocos años contestarán esta pregunta. Al presente parececuerdo tratar con quimioterapia con reactores recien virados en grupos altamente expuestos y los reactores virados recientemente en edades más vulnerables.

RESUME

Le talon d'Achille de la tuberculose, son point vulnérable réside dans sa curabilité dans la phase de début, son point fort réside dans sa capacité de multiplication due à la contagiosité des stades avancés. Une personne atteinte de tuberculose évolutive en infecte d'autres, et chacune d'entre elles en infecte d'autres, et ainsi de suite à l'infini. Le vieux terme qui s'appliquerait à ce phénomène serait "progression géométrique"; le terme moderne "réaction en chaine." L'individu atteint de lésions avancées crache des bacilles de Koch en plus grande quantité et est un contaminateur d'un plus grand pouvoir que celui qui, atteint de lésions minimes, ne crache que peu de bacilles ou n'en crache pas du tout.

En conséquence, pour juguler la tuberculose, il faut découvrir et traiter les formes à leur début, et éviter qu'elles n'arrivent à un stade avancé, principal facteur de contagion de la maladie! L'utilisation combinée des tests tuberculiniques, de la radiographie pulmonaire, et de la chimiothérapie réduira énormément la dissémination de l'affection. Le test tuberculinique sagement répété indiquera non seulement que l'infection est apparue, mais il indiquera également à quel moment et fréquemment à quel endroit; on pourra même connaitre la source de l'infection. Aussi bien, la radiographie pulmonaire doit-elle être répétée à intervalles appropriés, surtout à certains âges et chez des groupes d'individus particulièrement exposés, et chez tous les individus qui sont porteurs de réactions tuberculiniques positives, qu'elles soient récentes ou non.

L'auteur a la conviction que la tuberculose pulmonaire active minime devrait être traitée par la chimiothérapie. Il se demande à partir de quelles limites on peut se dispenser de traiter par la chimiothérapie une tuberculose minime. Les prochaines années donneront la réponse à cette question. En ce moment, il semble sage de traiter par la chimiothérapie les individus qui ont eu récemment un virage de leurs réactions tuberculiniques chez les groupes particulièrement exposés et chez ceux qui sont aux âges les plus vulnérables.

ZUSAMMENFASSUNG

Die Achillesferse der tuberkulösen Erkrankung, ihre verletzliche Stelle ist ihre Heilbarkeit in ihren frühen Stadien; ihre starke Seite ist ihre Fähigkeit zur Vermehrung vermöge ihrer Ansteckungs-fähigkeit in ihren fortgeschrittenen Stadien. Ein Mensch mit aktiver Erkrankung infiziert andere, und jeder von diesen infiziert wieder andere und so fort ad infinitum. Der alte Ausdruck dafür wäre die "geometrische Progression" gewesen, der moderne Ausdruck "Kettenreaktion." Die Person mit fortgeschrittener Erkrankung wirft mehr Tuberkelbazillen aus und vermag in stärkerem Masse die Krankheit zu verbreiten als jemand mit minimaler Erkrankung, der wenig oder keine Tuberkelbazillen auswirft.

Um die Tuberkulose zu bekämpfen, müssen wir daher den Frühfall entdecken und behandeln und daran hindern, der fortgeschrittene Fall, der Hauptverbreiter der Krankheit zu werden. Die kombinierte Verwendung des Tuberkulin-Testes, des Röntgenfilmes der Brust und die Chemo-Therapie werden die Verbreitung der Krankheit sehr stark vermindern. Der in erfahrener Weise wiederholte Tuberkulin-Test lässt nicht nur darauf schliessen, dass eine Infektion stattgefunden hat, sondern auch, *wann* sie erfolgt, und häufig, *wo* sie erfolgt ist, und sogar die *Quelle* dieser Infektion. In gleicher Weise muss die Brustkorb-Röntgenaufnahme in entsprechenden Abständen wiederholt werden, besonders in gewissen Altersklassen und bei stark exponierten Personengruppen, bei allen denjenigen mit positiver Reaktion unbeschadet dessen, ob der Umschlag neu ist oder nicht! Die Überzeugung ist eingewurzelt, wonach minimale aktive Lungentuberkulose mit Chemo-Therapie zu behandeln ist. Aber wie gering muss eine Tuberkulose sein, ehe man sie nicht mit Chemo-Therapie behandeln muss? Die nächstfolgenden Jahre werden diese Frage beantworten. Gegenwärtig scheint es ratsam, frisch Tuberkulin positiv gewordene Fälle in stark exponierten Gruppen und frisch Tuberkulin-positiv gewordene in besonders anfälligen Altersklassen mit Chemo-Therapie zu behandeln.

A Clinical Evaluation of the Effectiveness of Robitussin* in Chronic Cough**

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Since cough in chronic pulmonary disease may be of varied origin and etiology, proper treatment necessitates an accurate diagnosis and an attempt to correct the pathological mechanisms responsible for the cough in each individual patient. However, as long-term therapy is often necessary to accomplish this, symptomatic treatment of the cough may be indicated to afford the patient more immediate relief.

For the symptomatic approach to treatment, cough may be classified as either productive or on-productive.[1] Non-productive cough should be repressed as it serves no useful purpose and is bothersome and fatiguing to the patient. On the other hand, a productive cough is a beneficial one as it serves to remove accumulated secretions from the bronchial tree. Therefore, rather than suppressing it, it should be enhanced whenever possible.[2] This is especially true when the accumulated secretions are so sticky and viscid that they can be raised only with great difficulty and with undesirable expenditure of energy by the patient. This results in increasing fatigue which may lead to a state of "Tussal Insufficiency" with its complications as described by Banyai.[3]

Expectorant cough medicines are often of value in reducing tenaciousness of sputum and thus facilitating its removal by the normal cough reflex.[1, 2, 3] In a comparative study of the effectiveness of several commonly used expectorant cough remedies, Cass and Frederik[4] found that Robitussin®, a preparation containing 100 mgm. of glyceryl guaiacolate and 1 mgm. of desoxyephedrine hydrochloride in each 5 cc., was significantly superior to the other preparations studied. Blanchard and Ford[5] administered Robitussin to 76 infants and children with various types of upper respiratory infections including 21 with pertussis. They found this medication to be an effective preparation in the treatment of cough in childhood, and in those patients with pertussis, the severity and number of cough spasms were reduced at least 50 per cent and their duration definitely shortened.

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*Robitussin was supplied by the A. H. Robins Co., Richmond, Virginia.

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The present study was undertaken to determine the effectiveness of Robitussin as an expectorant in productive cough due to chronic pulmonary disease.

Material and Method

A total of 100 patients was studied consisting of 66 institutionalized with pulmonary tuberculosis and 34 out-patients, 13 with bronchiectasis and 21 with chronic bronchitis. The age range was from five to 72 years. All had in common a chronic productive cough but had difficulty in raising sputum because of its tenaciousness.

Only those with pulmonary tuberculosis were selected for study who had a residual cough after a minimum of two months of specific treatment of their disease with bed rest and chemotherapy. Such treatment was then continued unchanged throughout the ensuing study period. In respect to those with bronchiectasis and chronic bronchitis, the study was deferred if and whenever necessary until acute exacerbations of their disease had subsided under specific treatment and the cough had become stabilized. No medication except that under investigation was then administered during the testing periods.

Two separate studies were made. In the first, 50 patients—30 with pulmonary tuberculosis, eight with bronchiectasis and 12 with chronic bronchitis—were given Robitussin during three two-week periods which were separated by two interval or resting periods of one week each during which no medication was given. Using the pre-test period and subsequent interval periods to estimate the character of the cough in each patient, a base-line was set up in each instance from which to evaluate observations in the succeeding testing periods in which the medication was administered. In two with pulmonary tuberculosis, the cough disappeared completely during the course of the study and did not return in the interval periods. Since it could not be determined that the clearing of the cough was definitely due to the medication under investigation, these patients were dropped from the study. Therefore, for the 50 patients studied, a total of 150 observations was made. The effects of medication on tenaciousness of the sputum, frequency of the cough and over-all severity of cough were determined in each testing period and recorded as follows:

Marked improvement.
Moderate improvement.
Slight improvement.
No change.
Worsening.

Undesirable side effects which might be attributable to the medication such as anorexia, nausea, vomiting, dryness of the mouth, nervousness, insomnia, etc., were noted if and when they occurred.

The second study also comprised a total of 50 patients—36 with pulmonary tuberculosis, five with bronchiectasis, and nine with chronic

bronchitis. The format of this study was similar to the first except that a placebo medication was administered during the two interval periods. With the character of the cough in the pre-test period serving as a baseline, results were evaluated for the medication under investigation and for the placebo. A comparison of the results obtained with each could then be made. The placebo used was the plain aromatic syrup vehicle of Robitussin.

The dosage of Robitussin and the placebo used in the study was the recommended one of 1 to 2 drams every two to three hours as necessary. In most instances, the patients kept the medicine at their bedside and administered it to themselves.

Throughout both studies, observations were made by the attending physicians and nurses as frequently as possible but the patients' own opinions were given primary consideration as neither of the former could observe the patients constantly throughout the entire study period even when the patients were institutionalized. Obviously then, the study was primarily a subjective one. However, it was felt that if a relatively large number of patients was studied, the findings would be significant.

Objective evidence in a study of this kind is most difficult if not impossible to obtain. Chest x-ray films, blood counts, urinalyses, sedimentation rates and bacteriological examinations of the sputum were done routinely on each patient before and after the study periods but it was not expected that they would show any change which could be attributed to the medication under study. While initially, 24 hour sputum volumes were measured for each patient, no significant correlation between the effectiveness of the cough medication and the sputum volume could be established. This is in accord with conclusions reached by previous investigators.[4, 6, 7] In as far as we were able to determine, there is no simple and accurate method of measuring sputum viscosity and no attempt was made to do so in this study.

Results

The results of the first study are shown in Table I. It will be noted that Robitussin was in some measure effective in reducing the over-all severity of the cough in 82.7 per cent of the 150 testing periods. The medication was especially effective in loosening secretions and thus facilitating raising of sputum (80 per cent of testing periods) and was definitely effective, but to a lesser degree, in reducing the frequency of the cough (54.7 per cent of the testing periods).

In Table II, the results of the second study in the 150 testing periods in which Robitussin was administered are again tabulated. The findings were quite comparable to those obtained in the first study. There was an over-all improvement in the severity of the cough in 80 per cent of the testing periods. Again, the most marked effect of the medication was in reducing the tenaciousness of the sputum (74.7 per cent of the testing periods) but was also effective in reducing the frequency of the cough. (59.3 per cent of the testing periods.) There was an increase in the severity

TABLE I
EFFECTS OF ROBITUSSIN ON COUGH IN 150 TESTING PERIODS (50 PATIENTS). FIRST STUDY

	Tenaciousness of Sputum		Frequency of Cough		Over-all Severity of Cough	
	No. of Periods	Per Cent	No. of Periods	Per Cent	No. of Periods	Per Cent
Improvement	120	80.0	82	54.7	124	82.7
Marked	22	14.7	10	6.7	16	10.7
Moderate	64	42.7	25	16.7	66	44.0
Slight	34	22.6	47	31.3	42	28.8
No change	30	20.0	68	45.3	26	17.3
Worsening	0	0	0	0	0	0

TABLE II
EFFECTS OF ROBITUSSIN ON COUGH IN 150 TESTING PERIODS (50 PATIENTS). SECOND STUDY

	Tenaciousness of Sputum		Frequency of Cough		Over-all Severity of Cough	
	No. of Periods	Per Cent	No. of Periods	Per Cent	No. of Periods	Per Cent
Improvement	112	74.7	89	59.3	120	80.0
Marked	26	17.3	4	2.7	21	14.0
Moderate	51	34.0	33	22.0	60	40.0
Slight	35	23.4	52	34.6	39	26.0
No change	38	25.3	58	38.7	27	18.0
Worsening	0	0	3	2.0	3	2.0

TABLE III
EFFECTS OF ROBITUSSIN ON COUGH IN 300 TESTING PERIODS (100 PATIENTS). FIRST AND SECOND STUDIES

	Tenaciousness of Sputum		Frequency of Cough		Over-all Severity of Cough	
	No. of Periods	Per Cent	No. of Periods	Per Cent	No. of Periods	Per Cent
Improvement	232	77.3	171	57.0	244	81.3
Marked	48	16.0	14	4.7	37	12.3
Moderate	115	38.3	58	19.3	126	42.0
Slight	69	23.0	99	33.0	81	27.0
No change	68	22.7	126	42.0	53	17.7
Worsening	0	0	3	1.0	3	1.0

TABLE IV
COMPARATIVE EFFECTS OF ROBITUSSIN AND PLACEBO ON COUGH. EXPRESSED IN PERCENTAGE OF TESTING PERIODS

	Tenaciousness of Sputum		Frequency of Cough		Over-all Severity of Cough	
	Robitussin	Placebo	Robitussin	Placebo	Robitussin	Placebo
	Per Cent	Per Cent	Per Cent	Per Cent	Per Cent	Per Cent
Improvement	74.7	24.0	59.3	31.3	80.0	34.0
Marked	17.3	0	2.7	0	14.0	0
Moderate	34.0	10.7	22.0	14.0	40.0	10.7
Slight	23.4	13.3	34.6	17.3	26.0	23.3
No change	25.3	73.0	38.7	66.7	18.0	64.0
Worsening	0	3.0	2.0	2.0	2.0	2.0

and frequency of the cough in one patient throughout all testing periods with the medication and with the placebo. This patient had far-advanced pulmonary tuberculosis and shortly succumbed to his disease. We did not feel that his cough was made worse by the medication.

It might be presumed that the results of the first study would be more accurate than those of the second, as in the former, the base-line from which to evaluate the effect of the medication on the cough was reestablished in each of the interval periods to take into account any change in the character of the cough which might have resulted from other causes. However, since the results of the two studies were so comparable, this factor evidently was of no great significance, probably because of the manner in which the patients were selected for the study.

Table III is a combined tabulation of the results of both studies. As will be noted, improvement in the over-all severity of the cough occurred in 81.3 per cent of the 300 testing periods and the most significant effect was in the reduction of the tenaciousness of the sputum (77.3 per cent of the testing periods).

In Table IV, the effects on the cough of the medication and the placebo are compared. To avoid confusion, the values are expressed as percentages since the total number of testing periods in which each was administered differed. Thus, each value in the table refers to the percentage of the total number of testing periods in which the medication or the placebo was administered. It will be noted that in all respects, the medication was significantly superior to the placebo. However, it is evident that the placebo was also of some benefit both in decreasing tenaciousness of sputum and in reducing frequency of cough. This is not surprising for it has long been known that simple syrups exert a soothing effect on coughs. This is probably due to their action in increasing the volume of respiratory tract secretion.[8]

No severe undesirable side-effects of the medication were noted in either of the studies. Three patients complained that the medication was too sweet, in one to a degree which produced anorexia and nausea. However, this was only transient and it was felt not primarily due to the cough remedy as the patient continued on the medication throughout the remainder of the study without further complaint.

It is significant that 11 of the 13 patients with bronchiectasis reported that postural drainage was made more effective by the medication. Accumulated secretions in the bronchial tree were removed more freely and completely and in a shorter period of time. This was undoubtedly due to the action of the medication in rendering the sputum less viscid.

Practically all the patients included in the investigation had used various other cough remedies prior to the study and the majority of them expressed a preference for Robitussin as to effectiveness, taste and absence of undesirable side-effects.

Discussion

The predominant effect of Robitussin in this study was in rendering the sputum less viscid and thus easier to raise, corroborating the reports of previous investigators.[4, 5] Experimental evidence indicates that this action is brought about by an increased elaboration of respiratory tract fluid which dilutes and lowers the viscosity of the accumulated secretions in the bronchial tree.[7, 9, 10, 11] While the glyceryl guaiacolate constituent of Robitussin is chiefly responsible for this action, the simple syrup vehicle also significantly contributes as has been stated by Boyd[8] and supported by the findings of the present study. In comparing the effectiveness of many commonly used expectorants on respiratory tract fluid, Boyd et al.[9, 11] found that the action of glyceryl guaiacolate was the most intense and sustained, increasing the secretion of respiratory tract fluid nearly 200 per cent. The decrease in tenaciousness and viscosity of secretions brought about by this action increases the efficiency of the cough reflex and ciliary action in removing accumulated secretions from the trachea and bronchi.

In the present study, Robitussin was also found to be significantly effective in reducing the frequency of cough. This action is no doubt chiefly due to the effect of glyceryl guaiacolate and the syrup vehicle in enhancing the effectiveness of the cough reflex and ciliary action in the trachea and bronchi as described in the preceding paragraph but is also due in part to a local demulcent action of the increased respiratory tract fluid on the mucosa of the bronchial tree.[12] In addition, the aromatic syrup vehicle exerts a soothing effect on coughs arising in the pharynx by stimulating an increased production of mucus and saliva.[13]

The use of an effective expectorant such as Robitussin to help clear the bronchial tree of tenacious secretions and to reduce the frequency and severity of cough spasms is an important factor in the treatment of chronic pulmonary disease. Bronchiectasis and/or atelectasis may result from an accumulation and retention of mucus and purulent exudate in the bronchi.[3] Olsen and Clagett[14] have stated that, "There is probably a correlation between the retention of such secretions and the development of pulmonary osteoarthropathy (in bronchiectasis)." A severe and frequent cough is exhausting to the patient and may hinder his recovery. This is especially true in pulmonary tuberculosis where rest, both physical and mental, plays such a vital role in the treatment. A severe cough also seriously interferes with the process of repair in the lungs by destroying the healing fibrils as they form. Pinner[15] has stated that, "There is good clinical evidence for the assumption that the character of the cough is one factor determining the likelihood of intrabronchial spread (of tuberculosis). A patient with minimal cough and expectoration who has no difficulties in raising his sputum appears to be much less likely to develop intrabronchial spread than a patient with spasms of harassing cough who has great difficulties in clearing his bronchial tree of secretion. The latter will frequently find it necessary, from sheer physical exhaustion, to interrupt his cough before its natural and purposive termination is reached in expectorating sputum." Banyai[3] lists other possible complications of

severe coughing to be, "Pulmonary hemorrhage, spontaneous pneumothorax, vomiting, loss of appetite, exhaustion, headache, insomnia, rise in temperature, marked dyspnea, cyanosis, thoracic pain, fracture of ribs, mediastinal emphysema, subcutaneous emphysema, subconjunctival hemorrhage, urinary incontinence and indirectly, myocardial failure."

It is necessary that a cough medication produce no objectionable side reactions and that it be readily accepted by the patient. The fact that in the present study, Robitussin fulfilled these requirements in addition to being an effective expectorant, enhances its value in the treatment of chronic cough.

SUMMARY

1. It has been demonstrated that Robitussin exerted a significant beneficial effect in reducing the severity of chronic productive cough in 100 patients studied. In 50 patients to whom a placebo was alternately administered with the medication, the latter was significantly superior to the placebo.

2. The most striking effect of Robitussin was in reducing the tenaciousness of the sputum and thus rendering it easier to raise.

3. It also exerted a pronounced effect in reducing frequency of cough.

4. No significant undesirable side-reaction attributable to the medication was observed.

RESUMEN

1. Se ha demostrado que el Robitussin ejerce un efecto benéfico reduciendo la severidad de la tos crónica productiva en 100 enfermos. En 50 enfermos en quienes se empleó un placebo de modo alternativo con la medicación, ésta fué claramente superior al substituto.

2. El efecto más notable del Robitussin consistió en disminuir la tenacidad del esputo y al cambiar su consistencia permitir su fácil expectoración.

3. También ejerció un efecto pronunciado reduciendo la frecuencia de la tos.

4. No hubo efecto colateral indeseable que pudiese atribuirse a la medicación.

RESUME

1. Les auteurs démontrent que la "Robitussin" exerce un bienfait incontestable et a pu réduire, chez 100 malades étudiés, la gravité d'une toux chronique productive. Chez 50 malades, l'administration alternative de "placebo" et du médicament apporta la preuve incontestable de la supériorité de ce dernier produit.

2. L'effet le plus remarquable de la "Robitussin" fut la diminution de la consistance des crachats et la plus grande facilité de l'expectoration.

3. La médication a également une action nette sur la réduction de la fréquence de la toux.

4. Les auteurs n'ont observé aucune réaction secondaire notable qui puisse être attribuée à la médication.

ZUSAMMENFASSUNG

1. Es konnte nachgewiesen werden, dass Robitussin eine günstige Wirkung ausübt dadurch, dass es bei 100 untersuchten Kranken die Schwere eines chronischen produktiven Hustens linderte. Bei 50 Kranken, denen ein Placebo abwachselnd mit der Behandlung gegeben wurde, erwies sich die letztere als dem Placebo beträchtlich überlegen.

2. Die auffälligste Wirkung des Robitussins bestand darin, die Zähigkeit des Sputums zu vermindern und auf diese Weise das Abhusten zu erleichtern.

3. Es übte auch eine ausgesprochene Wirkung auf die Herabsetzung der Frequenz des Hustens aus.

4. Ins Gewicht fallende unerwünschte Nebenwirkungen, die auf die Medikation zu beziehen gewesen wären, wurden nicht beobachtet.

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Pericardial Celomic Cysts*

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Introduction

Pericardial celomic cysts, pleuro-diaphragmatic cysts, springwater cysts, serosal cysts, are all synonymous terms referring to the same pathological entity. They all refer to a thin walled cystic structure which usually lies on or near the diaphragm in the right cardiophrenic space. Because of their specific mode of origin and location attempts to classify them with other simple cysts of the pleura have been unsuccessful and they are necessarily assigned to a separate category.

Historical Background and Incidence

Although Dufour and Mourrut[1] are credited by some authors with the report of the first case in 1929, Drash and Hyer[2] cited a case of pleuro-pericardial cyst reported by Edwards[3] in 1927. Additional early reports were made by Pickhardt[4] in 1934, Freeman and Simon[5] in 1936, Weber[6] in 1934 and d'Abreu[7] in 1937. A review of the literature by Andrus and Heuer[8] in 1936 revealed only 15 cases of cysts of the mediastinum, other than dermoids and teratomas, have been reported. One of the largest series reported was that of Blades[9] in 1946. He found 10 cases of pleuro-pericardial cysts in 114 thoracotomies done in Army thoracic surgery centers for tumors of various kinds. Hughes[10] stated 14 of these cysts had been removed by the thoracic surgery staff at the Kennedy General Hospital. It is believed that this included many of the 10 cases reported by Blades.[9] Among the more recent reports are those of Kisner and Reganis[11] in 1949—one case, Lippert et al[12] in 1951—three cases, and Yelin, Gabriel and Abraham[13] in 1953—one case.

One would surmise from the relatively small number of cases reported that the occurrence of pleuro-pericardial cysts is uncommon. However, with the increasing number of routine chest surveys being done in schools, industrial plants, hospitals, etc., one may expect the incidence of reported cases to rise sharply.

Etiology

No unanimity of opinion exists with regard to the pathogenesis of pleuro-pericardial cysts. Of the numerous theories advanced by various authors, the one proposed by Lambert[14] appears the most plausible. Lambert pointed out that the pericardium arises from a series of disconnected lacunae which appear in early embryonic life. These lacunae, first seen in

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the mesenchyme lateral and ventral to the primitive streak, eventually enlarge and fuse to form the pericardial celom. This structure is at first an independent cavity, but gradually develops a communication with the pleuroperitoneal celom. As the embryo develops, the ligamentum transversum and ducts of Cuvier close this communication and divide the pleuroperitoneal celom into the pleural cavities above and the peritoneal cavity below. Failure of one or more of these normal processes of development may lead to congenital absence of the pericardium or congenital diaphragmatic hernia. Lambert holds that these reported cysts are due to failure of one of the primitive lacunae to merge with the others. It persists and develops into an independent cavity to form a cyst. Laipply[15] agrees with Lambert in regard to the origin of these cysts.

In contrast to this theory is that proposed by Kindred[16] as stated by Drash and Hyer.[2] These authors feel that morphologic evidence is available which suggests that these cysts originate by aberrant growths from the mesothelium of the pleural cavity as it invades the mesenchyme of the body wall.

Pathology

Characteristically these cysts are unilocular, thin walled, and contain clear fluid. The majority appear in the anterior mediastinum adjacent to the pericardium, diaphragm and lung. The microscopic appearance is that of a thin walled fibrous tissue sac lined by endothelial or mesothelial cells.

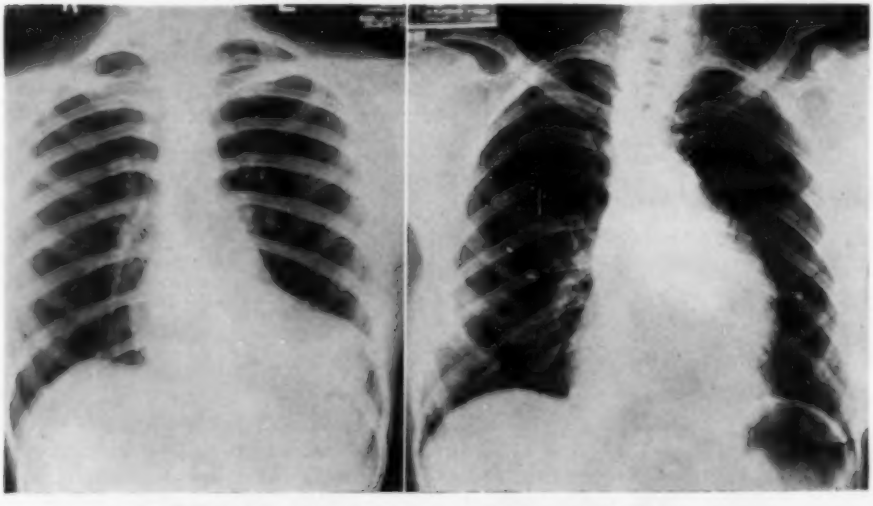

FIGURE 1 FIGURE 2

Figure 1 (*Case 1*): On this PA chest film there is a mass in the left lower chest which cannot be distinctly separated from the heart shadow.—*Figure 2* (*Case 2*): This PA chest film shows a smooth mass at the left hilar border which is continuous with the cardiac shadow.

Symptoms

The majority of pericardial cysts are asymptomatic. When symptoms do occur they are usually the result of increased pressure within the thoracic cavity with resulting compression of the heart, lungs, or mediastinal structures. Pickhardt[4] in 1934 and Kisner and Reganis[11] in 1950 reported symptomatic cases which were completely relieved by surgical excision.

Diagnosis

Although pleuropericardial cysts are in themselves benign, an unequivocal diagnosis cannot always be made pre-operatively. Among the more common tumors which must be considered in the differential diagnosis are teratomas, dermoid cysts, lipomas, chondromas, lymphangiomas and sarcomas. All diagnostic methods available should be used to determine the benignity or malignancy of the tumor mass. Pneumothorax, roentgenography, angiocardiography, bronchoscopy and bronchography should be used as indicated. In those cases in which diaphragmatic hernia is suspected, fluoroscopic examination before and after pneumoperitoneum may prove of inestimable value. The final diagnosis, however, can only be made in many cases by exploratory thoracotomy.

Treatment

It is generally agreed that the treatment of pericardial celomic cysts is surgical removal. The procedure is not difficult and carries little risk

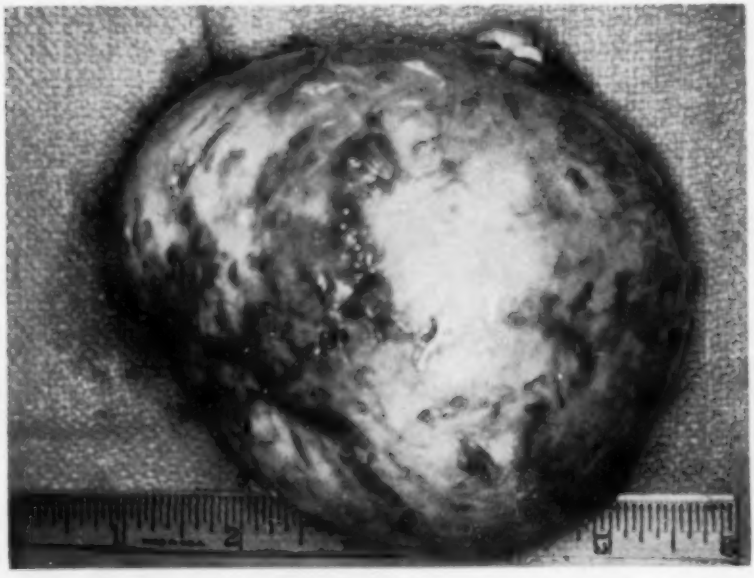

FIGURE 3 (*Case 2*): This is the operative specimen which measured about five inches in its greatest diameter.

to the patient. Drash and Hyer[2] cite three reasons for exploring all intrathoracic masses:

1. No mass can be confidently considered benign without biopsy.

2. The untoward mechanical effects of a space consuming lesion on the physiology of respiration and cardiac action.

3. Some benign lesions may cause complications by rupture into the bronchus or the pleura.

These indications are popularly accepted by many authors.

Case 1: O. M., a 25 year old white female was admitted to the Baptist Memorial Hospital, Memphis, Tennessee, August 14, 1951. A routine chest x-ray film had revealed a shadow in the left lower chest.

X-ray examination including a barium swallow showed no connection of the mass with the esophagus or stomach. A diagnostic pneumoperitoneum revealed the mass to be entirely within the thorax.

Routine physical examination was essentially negative except for decreased breath sounds over the left lower chest. A hemogram showed slight secondary anemia.

Operation: A 30 cm. segment of the left seventh rib was removed and the pleural space entered. A clear translucent cyst, 13 cm. in diameter was found lying between the posterior aspect of the pericardium and the median posterior aspect of the left diaphragm. Following combined blunt and sharp dissection the cyst was removed intact. Her postoperative course was satisfactory and she was discharged in good condition 10 days after operation.

Pathological Report: On gross examination, the cyst measured 13.5 by 9.5 by 2 cm. It was unilocular, thin walled and contained straw colored fluid. Microscopically the findings were compatible with pericardial celomic cyst.

Case 2: I. J., a 56 year old white woman was admitted to the Baptist Memorial Hospital on March 3, 1953. She was completely asymptomatic, a mass in the upper mediastinum having been noted on a routine x-ray film. Physical examination was

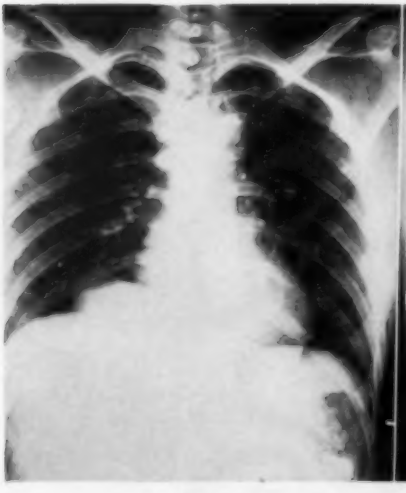

FIGURE 4

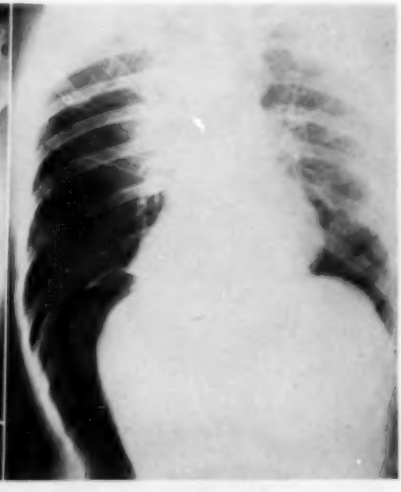

FIGURE 5

Figure 4 (Case 3): A Buckey film shows a smooth homogenous mass in the right cardiophrenic angle which appears to be intimately associated with both the pericardium and the right diaphragm.—*Figure 5 (Case 3):* A diagnostic pneumoperitoneum has been induced and a PA chest film made in the left lateral recumbent position. There is a suggestion of a triangular mass in the right cardiophrenic angle. The normal smooth curve of the heart in this area is missing.

essentially negative and routine laboratory work was within normal limits. X-ray examination revealed a mass in the upper mediastinum.

Operation: The chest was entered through the bed of the sixth rib on the left. A large pericardial cyst was found in the upper mediastinum with the lower extent at the level of the hilar region. A considerable extension between the pulmonary artery and aorta was present. The cyst was excised in toto. Postoperatively she did well except for slight hoarseness attributed to recurrent laryngeal nerve damage. She was discharged the eighth postoperative day.

Pathologic Report: On gross examination, the cyst measured 13 by 11 cm. with a smooth and glistening wall. Microscopic sections revealed a connective tissue membrane containing nerve bundles and blood vessels, consistent with pericardial cyst.

Case 3: T. McK., a 39 year old white woman was admitted to the Baptist Memorial Hospital, January 7, 1954. She gave a history of having chest pain following a throat operation in 1945. Six weeks prior to admission she had brought up a cupful of blood but could not say whether it was vomited or coughed up. She had run a low grade fever intermittently since 1945.

On routine physical examination nothing abnormal could be found in the chest. Routine postero-anterior chest films were read elsewhere as normal. X-ray studies taken here before and after diagnostic pneumoperitoneum revealed a lobulated mass in the right cardiophrenic angle. Routine laboratory studies were essentially negative.

Operation: (Performed by Dr. Robert McBurney) The right chest was explored through the bed of the seventh rib. A large pericardial cyst was found in the right cardiophrenic angle deriving its blood supply from the internal mammary artery. Following ligation of the vascular pedicle the cyst was removed in toto. She was discharged on the 10th postoperative day.

Pathologic Report: Grossly the cyst was thin walled, contained clear fluid and weighed 153 grams. A few areas of ecchymotic hemorrhage were present over the surface of the cyst wall. Histologically the tissue was compatible with a diagnosis of pleuropericardial cyst.

Case 4: L. C., a 43 year old white male was admitted to the Baptist Memorial Hospital February 1, 1954. A mass in the right chest had been detected on routine tuberculosis by a mobile x-ray unit.

Physical examination was essentially negative. X-ray studies including bronchograms revealed an extrapulmonary mass in the right anterior cardiophrenic angle. Routine laboratory work was normal.

Operation: On February 4, 1954, the right chest was explored through the sixth intercostal space. A pericardial cyst approximately 8 x 9 cm. in diameter was found adjacent to the pericardium in the right costophrenic sinus. No communication between the cyst and the pericardial cavity was demonstrated. The cyst was removed in toto. The postoperative course was uneventful and he was discharged 14 days after surgery.

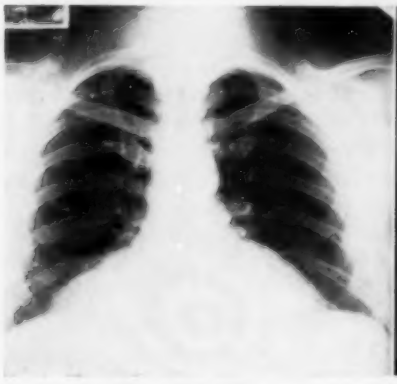

FIGURE 6

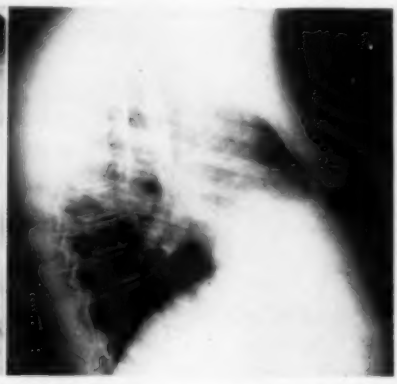

FIGURE 7

Figure 6 (Case 4): On the postero-anterior film there is evident a smoothly outlined homogenous mass in the right cardiophrenic angle which cannot be definitely separated from the cardiac silhouette.—*Figure 7 (Case 4):* The right lateral chest film demonstrates the mass to be located anteriorly in the chest just above the right diaphragm.

Pathologic Report: Grossly the cyst was thin walled, white and transparent, weighing 290 grams. On section 275 cc. of thin, clear fluid was found within the cyst. Histologically the tissue was compatible with pericardial cyst.

Case 5: J. W. G., a 39 year old white female was admitted to the Baptist Memorial Hospital, November 16, 1954. X-ray film of the chest two weeks prior to admission revealed a suspicious lesion in the lower lobe of the right lung. The remainder of the history was essentially negative. Physical examination revealed a mass in the right breast which biopsy showed as accessory breast tissue.

Operation: A 12 inch incision was made on the right side through the sixth intercostal space and the right hemithorax entered. A large pericardial celomic cyst at the cardiophrenic angle was noted. It was filled with clear watery fluid and measured approximately 8 cm. in its longest diameter. There was a direct communication with the pericardial sac through an opening approximately one-fourth inch in diameter. This sac was dissected free and the cyst excised. Postoperatively the patient did well and was discharged on the sixth postoperative day.

Pathological Report: Grossly the cyst consisted of a thin walled pinkish-gray membrane which was lined with thin grayish appearing tissue. Microscopic sections revealed a mesothelial lined cyst compatible with the clinical diagnosis of pericardial cyst.

Case 6: C. H., a 51 year old colored male was admitted to the John Gaston Hospital in Memphis, January 7, 1955. He gave a history of having noted bilateral subcostal pain of one year duration. There was no history of hemoptysis, dyspnea, cough except when he had a fresh cold.

Routine chest x-ray film had shown a mass in the left lower lung field. Physical examination was essentially negative. On fluoroscopic examination questionable pulsation of the mass was seen. Differential diagnosis revolved around myocardial aneurysm versus pericardial celomic cyst. X-ray film fluoroscopic studies showed the mass to be extra pulmonary in nature.

Operation: The left chest explored through the fifth intercostal space. A large pericardial celomic cyst was identified in the cardiophrenic angle. No communication between it and the pericardial cavity was demonstrated. The cyst was completely excised without difficulty. Postoperative course was uneventful and he was discharged on the eighth postoperative day.

Pathological Report: The gross examination was an irregular mass of fatty tissue appearing to be a collapsed cyst measuring 7 x 5 x 10 x 2 cm. The inner lining was composed of a layer of thin, translucent, shiny gray material. Microscopically the cyst wall was lined by a cuboidal to a flattened type of epithelium. Histologically the tissue was compatible with pericardial cyst.

SUMMARY AND CONCLUSIONS

Pericardial celomic cysts are uncommon in occurrence. No unanimity of opinion exists regarding their cause, although the theory that they result secondary to a developmental irregularity of the primitive lacunae, appears to be most feasible. When symptoms are present they are usually the result of mediastinal compression. Differential diagnosis should include elimination of such tumors as teratomas, dermoid cysts, lipomas and chondromas. The treatment of choice is surgical excision.

Six case reports of pericardial celomic cysts are presented.

RESUMEN Y CONCLUSIONES

Los quistes celómicos pericárdicos son poco comunes. No hay opinión unánime respecto de su causa aunque la teoría de emanan de una irregularidad en el desarrollo de las lagunas primitivas parece la más plausible. Cuando hay síntomas de tos resultan de la compresión mediastinal. El diagnóstico diferencial debe incluir la eliminación de los teratomas, quistes dermoides, lipomas y condromas. El tratamiento de elección es la extirpación quirúrgica. Se presentan seis casos de esos quistes.

RESUME

Les kystes coelomiques péricardiques ne sont pas exceptionnels en fait. L'unanimité des auteurs n'est pas faite en ce qui concerne leur étiologie, bien que la théorie selon laquelle ils seraient secondaires à une malformation des lacunes primitives apparaisse comme la plus vraisemblable. Lorsqu'il existe des symptômes, ils sont généralement en rapport avec la compression médiastinale. Le diagnostic différentiel devrait comprendre l'élimination des tumeurs tels que les tératomes, les kystes dermoïdes, les lipomes et les chondromes. Le traitement de choix est l'exérèse chirurgicale. Les auteurs rapportent six cas de kystes coelomiques péricardiques.

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNGEN

Coelomzysten am Perikard kommen selten vor. Über die Entstehungsursache herrscht keine Einigkeit, obwohl die wahrscheinlichste Theorie besagt, dass sie sekundär aus einer Entwicklungsstörung der primitiven Lacunae entstehen. Wenn Symptome auftreten, sind sie im allgemeinen Folgen einer mediastinalen Kompression. Die Differential diagnose sollte Teratome, Dermoidzysten, Lipome und Chondrome ausschliessen. Die Behandlung der Wahl ist chirurgische Exstirpation. Bericht über sechs Fälle von Coelomzysten am Perikard werden beschrieben.

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Localized Hypertrophic Emphysema

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Localized hypertrophic emphysema is the abnormal increase of volume of one lobe or part of one lobe of the lung owing to overdistention of the alveolar spaces. It is unassociated with aspiration of obstructing material and is a rather infrequent phenomenon. The earliest report was that of Wethered[1] who, in 1897, reported finding an emphysematous right upper lobe during necropsy on a 51 year old man. Since the right middle and lower lobes were free of anthracotic pigment the author conjectured that these latter lobes had collapsed during the patient's childhood causing compensatory enlargement of the right upper lobe. In 1938 Royes[2] cited the case of a 28 year old Hindu man who was killed instantly in a motorcar accident. At necropsy it was noted that a portion of the right middle lobe was enlarged. A small flap of mucous membrane was noted in the bronchus leading to the involved segment. This flap occluded about five-eighths of the bore of the bronchus at this point. A review of the English medical literature[3-10] published since 1938 revealed 18 cases which concerned a condition that actually was or closely resembled localized hypertrophic emphysema. This total does not include such cases of obstructive emphysema as were presented by Caffey[11] and Maxwell[12] in which either atelectasis and infection played a role or in which the emphysema represented an early stage in the development of atelectasis.

In most of the cases reported in the literature the patients have been infants or young children. A characteristic clinical picture is presented of respiratory distress and wheezing breath sounds in the absence of manifest respiratory infection. The respiratory difficulties may be severe enough to cause intermittent cyanosis. Inspiratory sternal and subcostal retraction is common.

On physical examination breath sounds are absent on the involved side. A hyperresonant percussion note is usually heard. Signs of partial consolidation may be elicited on the uninvolved side owing to compression of the normal lung by the expanded emphysematous lobe. Mediastinal shift will be manifested by displacement of the heart sounds to the uninvolved side.

The roentgenographic picture of the thorax is by no means pathognomonic. A large radiolucent area can be seen on the same side over which breath sounds were not heard. Careful examination of the lungs may reveal trabecular markings throughout the radiolucent side. Mediastinal shift and tracheal deviation are readily apparent.

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The pathologic aspects of localized hypertrophic emphysema have been well described by Shaw.[9] The disease is usually limited to either upper lobe or to the right middle lobe. The involved segment or lobe is enlarged to many times its normal size, the remaining lung being compressed but normal. Grossly the surface is smooth and pink. The diseased tissue does not collapse even when the bronchus to the region is left open. It also floats in water, only a small portion being submerged. The cut surface shows many small dilated alveoli within the spongy lung tissue.

Microscopic examination reveals distended and empty alveoli. The alveolar septa are thin and devoid of inflammation, and the small bronchi and bronchioles have normal intact epithelium and are free of exudate or secretion. The cause of the disease may not be apparent from the pathologic specimen.

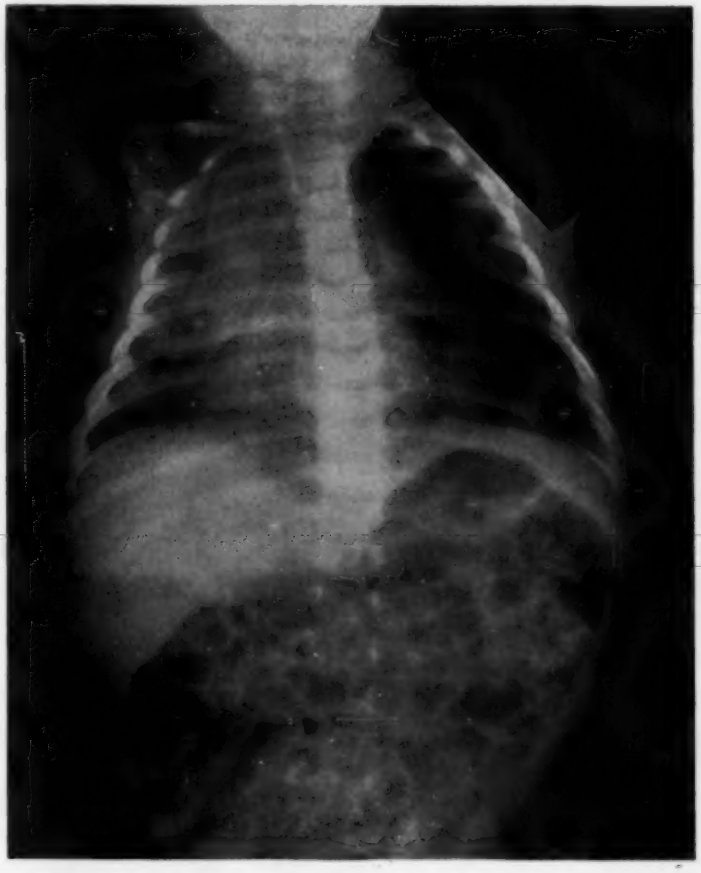

FIGURE 1: Roentgenogram of thorax at the time of the patient's second admission (Oct. 1, 1952) at the age of 2½ months. The cardiac shadow lies in the right hemithorax. The left side is more radiolucent than the right.

In the following report of a case the afore-mentioned criteria were fulfilled and a diagnosis of localized hypertrophic emphysema was suggested preoperatively and confirmed on pathologic examination of the specimen.

Report of Case

A white boy was born on July 17, 1952, after normal gestation. His delivery was difficult but he breathed spontaneously and did not require resuscitation. His weight at birth was seven pounds and five ounces. He was a feeding problem in that he seemed to have difficulty retaining food and often choked; respiration was labored.

The infant was brought to the Mayo Clinic on July 24, at the age of one week. At that time, his heart sounds were heard on the right side of the thorax. Breath sounds in the upper anterior part of the left side of the thorax were absent. A roentgenogram was made of the thorax (fig. 1) and a tentative diagnosis was given of dextrocardia or cystic left lung. Because the child did very well in the hospital, he was dismissed and the parents were instructed to bring him back for re-examination in three months.

The patient remained well until September 29 when rapid labored respirations developed. He was examined again at the clinic on September 30 and was found to have inspiratory retraction of the costal margin. Cyanosis was not discernible. A roentgenogram of the thorax taken the day after his admission showed evidence of marked emphysema of the left lung. Because of the possibility of endobronchial foreign body, bronchoscopy was performed. The left main and left lower bronchi were somewhat smaller than normal and seemed to be partially collapsed. Obstruction was not found. In the ensuing days the infant's condition improved considerably. It was felt that although thoracotomy might eventually be necessary, the child's excellent condition and normal development would permit deferment of surgical intervention until he was somewhat older. Subsequently he was again dismissed and his parents were strongly advised to return him for restudy in three months.

The child was examined again in January and in April, 1953, at the ages of six and nine months respectively. His growth and development were normal; he had no respiratory difficulties. Roentgenograms of his thorax did not show any significant change at either visit and he remained in good health. Congenital emphysema of the left upper lobe was suggested by one examiner. On May 11, 1953, he was admitted to the clinic with an acute febrile illness of two days' duration. Localizing signs were not present and roentgenograms of his thorax remained as before. His temperature returned to normal about 24 hours after his admission. The child continued to do well and was seen in August, 1953, and January, 1954.

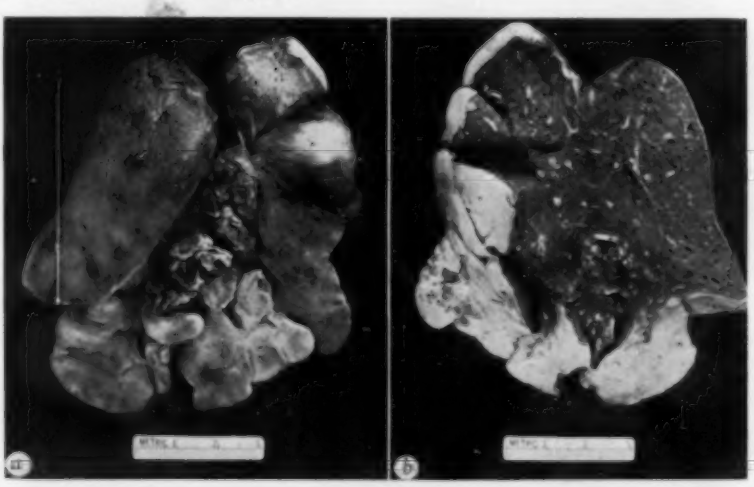

FIGURE 2A: Mediastinal surface of the resected left upper lobe. The lung tissue does not collapse despite the fact that its bronchi are open. No blebs are seen on the pleural surface.—FIGURE 2B: Cut surface of the specimen showing small scattered cystic spaces but no large cysts.

On March 11, 1954, thoracotomy was performed on the left side with the patient under endotracheal ether anesthesia. The left upper lobe occupied almost the entire left hemithorax, and did not collapse when the pleural space was opened. The uninvolved lingula and left lower lobe were normal but compressed. Lobectomy was performed on the upper lobe of the left lung. The patient's postoperative course was entirely uncomplicated.

The surgical specimen as received in the laboratory presented a striking gross appearance (fig. 2A). The lung tissue did not collapse even after the bronchi had been opened out. There were no blebs on the pleural surface. The lobe felt spongy, was resilient and floated on the surface of the formalin in which it was to be preserved.

The cut surface (fig. 2B) showed small (2 to 4 mm.) cystic spaces which were irregular in size, scattered, and contained only air. The bronchial tree was opened as far as possible grossly but obstruction or bronchial abnormalities were not found.

Microscopic examination of multiple sections of the involved part revealed large air-filled emphysematous alveoli (fig. 3A). The blood vessels, bronchi and bronchioles were normal in all respects. There was no inflammatory infiltrate. Stained sections (fig. 3B) revealed the elastic tissue to be normal both quantitatively and qualitatively.

Discussion

The etiology of localized hypertrophic emphysema is still in question although several theories have been proposed and various factors implicated. It is possible that several or none pertain to this disease.

Intermittent obstruction owing to a check-valve type of mechanism in the bronchus has been suggested as a causative factor by several authors. Flaps of mucous membrane or redundant mucosa in the bronchus leading to the involved region have been reported.[2, 5, 8] Several patients had partial bronchial obstruction due to ductus arteriosus or ligamentum arteriosum,[3] an anomalous vessel[8] or herniation of a lobe through a mediastinal defect.[8] It has been shown that partial bronchial obstruction with or without a check-valve mechanism can result in emphysema of the lung tissue sup-

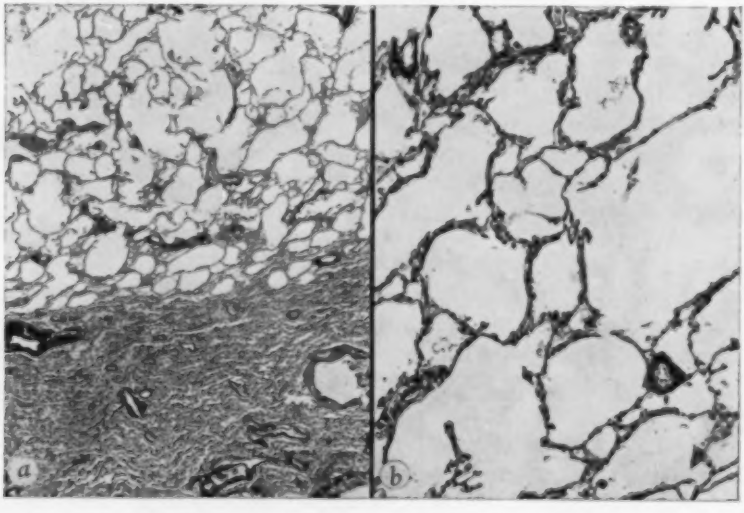

FIGURE 3A: Junction is shown between emphysematous lung and compressed normal lung (x23).—FIGURE 3B: Emphysematous lung tissue (x74). There is no inflammatory infiltrate. (Verhoeff's stain for elastic tissue counterstained with van Gieson's connective tissue stain.)

plied by that bronchus.[13, 14] Gordon,[13] however, points out that a bronchial check valve with more or less complete expiratory obstruction is likely to result in acute emphysema with a more rapid course than the emphysema associated with the disease under discussion.

Vigorous attempts at respiratory resuscitation immediately after delivery have been suggested as a cause.[5, 9] This, however, would be more likely to result in generalized interstitial pulmonary or mediastinal emphysema and possibly pneumothorax than in a strictly localized disease without perivascular dissection by air.[15] A history of such violence after delivery is not often obtained and was not a feature of the case herein reported.

Pulmonary infection with bronchial obstruction has been shown to cause regional obstructive emphysema in infants and children.[11] The diseased segment however, is more cystic in nature, may be filled with infected, inflammatory exudate and is usually surrounded by atelectatic tissue. The condition is reversible with proper conservative management.

Congenital factors intrinsic to the diseased region have been found in association with localized hypertrophic emphysema. In cases reported by Fischer and co-workers,[3] Overstreet,[7] Shaw[9] and Crossett and Shaw[16] some of the resected specimens showed abnormalities in the walls of the bronchi which consisted of complete absence or hypoplasia of cartilage[3, 9] or incomplete cartilaginous rings.[7] Shaw expressed the opinion that this abnormality is due to congenital chondromalacia localized to the emphysematous segment. The bronchial walls are flaccid and can be pulled open during inspiration. During expiration these bronchi collapse, entrapping air in the alveoli. This is in effect a check-valve mechanism and, as has been pointed out, would be more likely to lead to acute obstructive emphysema. We therefore hesitate to interpret the significance of the lack of bronchial cartilage since this abnormality is not found in all cases and was not found in the case herein presented.

In some of the reported cases, as in our case, even after an exhaustive search for bronchial obstruction, the cause of the disease has remained unknown. Robertson and James,[8] after an equally fruitless search for bronchial obstruction in one of their cases, speculated on the possible source of obstruction being left in the proximal portion of the bronchial stump. Such an occurrence does not seem likely in our case.

The treatment of choice is resection of the involved lobe or segments. The results of such treatment have been almost universally excellent as was true in the case we have presented.

SUMMARY

A case of localized hypertrophic emphysema affecting part of the left upper lobe of a child has been reported. Treatment consisted of surgical resection of the diseased tissue.

The examination of gross specimens revealed characteristic pathologic findings. The lung tissue did not collapse when the bronchi were opened

as it does in the normal lung. The alveoli were dilated and enlarged but the bronchial tree appeared to be entirely normal.

A review of the literature revealed 18 cases of localized hypertrophic emphysema or a condition closely resembling it. As yet the cause of the disease is not established and various etiologic factors have been suggested. Several or none of these factors may be implicated in any particular case.

RESUMEN

Se refiere un caso de enfisema localizado hipertrófico en el lóbulo superior izquierdo de un niño. El tratamiento consistió en resección del tejido enfermo. El examen de la pieza reveló hallazgos característicos. El tejido pulmonar no se colapsó cuando se abrieron los bronquios como sucede en el pulmón normal. Los alveo los estaban dilatados y crecidos pero el árbol bronquial parecía enteramente normal.

Una revisión de la literatura hizo descubrir 18 casos de enfisema localizado hipertrófico y una condición muy parecida. No se ha establecido aún la causa de la enfermedad y varios factores etiológicos se han sugerido. Varios o ninguno de estos factores pueden encontrarse en cualquier caso.

RESUME

Les auteurs rapportent un cas d'emphysème hypertrophique localisé à la partie supérieure du lobe gauche chez un enfant. Le traitement consista dans la résection chirurgicale du parenchyme atteint.

L'examen macroscopique des pièces permis de constater des lésions caractéristiques. Contrairement à ce qui se produisit dans le poumon normal, l'ouverture des bronches n'amena aucun collapsus. Les alvéoles étaient dilatées et augmentées de volume, mais alors que les bronches se montraient tout à fait normales.

Une revue de la littérature révéla 18 cas d'emphysème hypertrophique ou d'état lui ressemblant. Jusqu'à présent la cause de cette affection n'a pas été établie et différents facteurs étiologiques ont été invoqués. Dans chaque cas particulier, tantôt on trouve réunis plusieurs de ces facteurs, tantôt on ne peut mettre aucun d'entre eux en évidence.

ZUSAMMENFASSUNG

Bericht über einen Fall eines umschriebenen hypertrophischen Emphysems, das einen Teil des linken Oberlappens eines Kinds betraf. Die Behandlung bestand in chirurgischet Resektion des erkrankten Gewebes.

Die Untersuchung makroskopischer Proben ergab charakteristische pathologische Befunde. Das Lungengewebe kollabierte nicht nach Eröffnung der Bronchien, wie dies bei der normalen Lunge der Fall ist. Die Alveolen waren erweitert und vergrössert, jedoch hatte der Bronchialbaum ein ganz normales Aussehen.

Eine Durchsicht der Literatur ergab 18 Fälle eines umschriebenen hypertrophischen Emphysems oder einer ihm sehr ähnlichen Veränderung. Bisher steht die Krankheitsursache noch nicht fest, und es werden ver-

schiedene aetiologische Faktoren vermutet. In jedem Einzelfall können mehrere oder überhaupt keine dieser Faktoren einbezogen sein.

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Five Year Follow-up of Thirty-four Resections for Pulmonary Tuberculosis

JOSEPH F. TEDESCO, M.D., F.C.C.P.
Castle Point, New York

In an attempt to evaluate the results of excisional surgery in pulmonary tuberculosis a study was done on all patients who underwent resections at Veterans Administration Hospital, Castle Point, New York over five years ago. A total of 34 patients were operated upon, eight in 1947 and 26 in 1948. The information that was required to complete this study was obtained from the various Veterans Administration Regional Offices designated to handle the post-hospital follow-ups as well as from the individual patients.

A review of the medical literature failed to disclose similar studies in pulmonary resections which were performed over five years ago.

Present Status of Patients

Twenty-seven of the 34 patients are now classified as inactive and are either working or attending school. Deaths have occurred in four of the other seven. Three of the deaths were attributed to the surgical procedure, one in the early post-operative and two in the late post-operative period. The other death followed an acute coronary occlusion, 20 months following resection. The other three are now receiving treatment following re-activations of disease.

The accompanying table lists the following information according to type of resection performed, previous pneumothorax, previous thoracoplasty; streptomycin prior to and after surgery; sputum status before resection; pathological findings in resected lung; concomitant decortication, and number of failures.

Remarks on Accompanying Table

Some form of collapse therapy, either medical or surgical was performed in 28 of the 34 patients without conversion of sputum to negative before resection. Six of the 28 were first given pneumothorax before thoracoplasty was done. A total of 17 (50 per cent) of all the cases in this study were thoracoplasty failures. Eleven of the 17 are now doing well; four of the other six have died while two are receiving treatment for active disease.

Only eight patients had received an additional course of streptomycin prior to the course that was administered in conjunction with excisional surgery. These courses ranged from 27 to 123 days.

The administration of streptomycin pre-operatively was limited to short courses of 1.0 gm. daily, two to 42 days. Three upon whom pneumonectomies were done did not receive streptomycin until the date of re-

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section. Two of the three patients had an isolated positive sputum post-operatively, one at four months and the other at eight months. Streptomycin was discontinued in these two 85 and 60 days post-resection respectively.

Post-operative courses of streptomycin were limited to short courses of 1 gram daily. The longest course was 112 days.

Sputum was positive for tubercle bacilli in 29 of the 34 patients pre-operatively. One of the 29 was positive two months before pneumonectomy was done in a thoracoplasty failure.

Discussion

The evaluation of the results of any form of treatment in pulmonary tuberculosis is difficult in view of the chronicity of the disease with re-activation in some cases after years of inactivity. A five year period was selected as a satisfactory period of observation. Fortunately, it was possible to obtain the necessary information on all 34 patients.

The results are considered gratifying because 27 of the 34 resections were done after failure of previous collapse treatment and prolonged periods of hospitalization. Twenty-seven are now considered inactive and have been returned to some gainful activity at home. The occurrence of three post-operative deaths and three re-activations of disease compares favorably with results of other forms of treatment.

The administration of streptomycin for short periods pre-operatively was in accordance with the practice at that time. It is presumed that the tubercle bacilli were not resistant to streptomycin in most cases since only short courses were given pre-operatively. Unfortunately sensitivity studies were not done at that time. One can only conjecture whether the low incidence of broncho-pleural fistulae was due to presence of chemotherapy protection when it was needed the most. Only one had a proved broncho-pleural fistula and in that case the operation was a difficult resection following thoracoplasty. During removal the cavity wall was inadvertently lacerated. Two others developed draining sinuses with abscesses which might have been due to unrecognized bronchial leaks.

On the other hand, the occurrence of positive sputa post-operatively in 11 can probably be attributed to the termination of chemotherapy after short courses following surgery.

This patient then received 1 gram of streptomycin daily. The resected lung showed scattered fibroid deposits without evidence of cavity or other active disease.

Lobectomy was performed in three of the five who had negative sputa pre-operatively. Segmental resection was done in the other two. In one case an open cavity (probably tuberculous), 2 cm. in diameter was present in the resected segment. In the other four, encapsulated caseous foci, 1 to 3 cm. in diameter were present in the resected material. In one of them, lobectomy was done because of marked stenosis of the right lower lobe bronchus which was confirmed by the pathologist.

Failures

Four have died and three are receiving treatment for re-activations of disease. Brief summaries follow:

M. C., a 35 year old white male was admitted October 29, 1947. Streptomycin 1.0 gram daily, was given from February 29, 1948 to June 3, 1948. Right thoracoplasty was done in May 1948. Sputum remained positive. Streptomycin 1.0 gram daily was re-instituted on November 16, 1948. Right pneumonectomy was done seven days later. The azygous vein was divided in order to free the upper lobe. He developed severe dyspnea 36 hours postoperatively. Thoracentesis was done removing 525 cc. of sanguinous fluid. He died four hours later (November 25, 1948). Post-mortem examination was not done. The resected lung contained a cavity in the upper lobe and caseous foci in the middle and lower lobes.

J. G., a 30 year old white male was admitted July 18, 1948. He received 2.0 grams streptomycin daily from September 5, 1947 to October 26, 1947. Left thoracoplasty was done October 14, 1947. Streptomycin 1.0 gram daily was started on May 11, 1948 and continued until date of death (August 25, 1948). Sputum was positive for tubercle bacilli pre-operatively and on June 16, 1948. Left pneumonectomy was done on May 25, 1948. At the time of surgery the apex could not be completely freed. A clamp was applied as far up as possible and lung removed by dissecting proximal to the clamp. A calcified area of tissue remaining in the apex was packed with absorbable gauze. The resected lung contained a cavity in the left apex. Empyema developed and the fluid contained chyle with 80 to 95 per cent lymphocytes on repeated examinations. Cultures of the fluid were negative for tubercle bacilli. Post-mortem examination was not done.

E. E., a 29 year old white male was admitted May 10, 1946 with bilateral involvement and positive sputum. Left pneumothorax was induced four months before admission. Streptomycin 1.0 gram daily was given from March 11, 1948 to May 1, 1948. Right thoracoplasty was done on April 16, 1948. Sputum remained positive and right upper and middle lobectomy was done on October 22, 1948. Streptomycin 1.0 gram daily was given from October 21, 1948 to December 20, 1948. The cavity wall was entered during the operation. A broncho-pleural fistula and empyema developed on February 1, 1949. Streptomycin 1.0 gram daily was given from February 4, 1949 to date of death (March 18, 1949). On post-mortem examination an open bronchial stump with empyema was found on the right side.

The other death occurred in a 31 year old colored male 22 months after right upper and middle lobectomy was done in a thoracoplasty failure. He was discharged from the hospital as an arrested case on July 8, 1949 and died on January 21, 1950 following coronary occlusion.

Three patients are receiving treatment for re-activations:

W. M., a 45 year old white male was admitted July 17, 1946. Three stage thoracoplasty was done in April and May 1948. At time of resection numerous nodular foci were felt in the base of the right lower lobe. A cavity was present in the resected upper lobe. Infiltration on left side increased after lobectomy. He received streptomycin 1.0 gram daily from October 28, 1948 to February 9, 1949. Sputum remained positive until October 1948. PAS 12.0 grams daily was given from June 9, 1949 to October 6, 1949. He was discharged on October 16, 1950 apparently arrested. In November 1951 an abscess developed in the anterior end of the incision. He was readmitted to Castle Point on December 18, 1951. Streptomycin 1.0 gram and PAS 12.0 grams daily were started on January 26, 1952. Streptomycin dose was reduced to 1.0 gram twice weekly on July 26, 1952. PAS was discontinued in November 1952. He was discharged with maximum hospital benefit on December 19, 1952. INH 300 mgm. daily was added to streptomycin on September 21, 1953 after sputum culture in June, 1953 was positive. X-ray film in September 1953 showed infiltration with possible cavity in right lower lung field.

E. R., a 40 year old white male was admitted September 30, 1946. Right pneumothorax was induced in October 1946. Streptomycin 1.0 gm. daily was started on July 11, 1947 and increased to 2.0 grams daily on November 11, 1947. He left against medical advice on November 11, 1947. He was re-admitted on April 14, 1948. Streptomycin 1.0 gram daily was re-started on June 11, 1948. Right upper lobectomy was done on June 18, 1948. The resected lobe contained numerous caseous foci 0.3-1 cm. in diameter. Inactive disease was present on the opposite side. Streptomycin was discontinued on July 2, 1948. Four rib thoracoplasty was done on October 15, 1948. He left without leave in January 1949. In April 1950 he developed an abscess in the right axilla which was attributed to sutures. Since that date he has been admitted three times to WaWa Chest Hospital. Spreads of disease have occurred first on the right

side and then in the left upper lobe. Sputum was still positive early in 1954 with cavity in left apex.

R. D., a 41 year old white male was admitted May 10, 1947. Right thoracoplasty was done on March 9, 1948. Sputum remained positive. The right upper lobe and a wedge from the lower lobe were removed on November 30, 1948. Cavity was present in both resected tissues. Streptomycin 1.0 gram daily was given from November 28, 1948 to January 20, 1949. Inactive disease was present on left side at time of surgery. Sputum remained positive and dehydrostreptomycin 0.5 gram daily and PAS 12.0 grams daily were given from February 6, 1950 to March 24, 1950 for a laryngeal ulcer. He was discharged with maximum benefit on June 9, 1950 as an active case. In December 1952 there was evidence of cor pulmonale (edema of legs and dyspnea). He was admitted to Veterans Administration Hospital, Brooklyn, New York on January 24, 1953. Streptomycin 1.0 gram twice weekly and INH 300 mgm. daily were started on December 2, 1953. He was transferred to Castle Point on August 12, 1953. Tomograms showed a cavity on the left side. Isoniazid and streptomycin were continued until January 21, 1954 when PAS was substituted for streptomycin. His condition has deteriorated slowly and prognosis is poor.

Complications

In the remaining 27 patients the post-operative course did not present serious complications. Eleven had isolated positive sputa post-operatively, in one case as late as the 13th month.

In eight cases x-ray films did not show evidence of fresh disease which would account for the positive sputum. One who had active disease with possible cavity in the opposite lung pre-operatively only received streptomycin for one month after lobectomy. After surgery sputum culture

Type of Resection	Pneumonectomy	Lobectomy	2 Lobes Removed	Lobectomy and Wedge	Segmental
Number of Cases	15	13	3	1	2
Previous PNX	4	6	1	0	0
Previous TCP	7	2	1	1	0
Previous PNX and TCP	4	1	1	0	0
No Collapse	0	4	0	0	2
Previous SM	5	2	1	0	0
Gms. SM—Ave Dose	80	106	51	0	0
Number of Days SM	27-121	89-123	51	0	0
Day SM—Pre-op.	(12 pts.) 4-42	2-21	2-14	3	8-11
Ave Dose SM—Pre-op.	15	8	8	3	9
Days SM—Post-op.	2-112	13-103	14-59	53	9-26
Ave Dose SM—Post-op.	55	41	36	53	17
Positive Sputum Pre-op.	15	10	3	1	0
Pathology in Resected Tissue					
(a) Open Cavity	11	7	3	1	2
(b) Encapsulated	3	6	0	0	0
(c) No Active Disease	1	0	0	0	0
Decortication at time of Resection	0	5	1	0	0
Deaths	2	0	2	0	0
Still Active	0	2	0	1	0

was positive in the seventh month and again in the 13th month. Subsequently sputum remained negative with clearing of disease on opposite side without additional chemotherapy.

One developed a spread of disease with two positive sputum concentrates four months after pneumonectomy. This spread cleared without additional chemotherapy and sputum converted.

Another developed a fresh infiltration eight days after pneumonectomy. Streptomycin was discontinued 40 days after resection. Two positive concentrated sputa were detected three months after surgery. Streptomycin 1.0 gram daily was then given for 90 days with conversion of sputum.

One developed a spread three weeks after pneumonectomy, however, sputum remained negative. Two courses of streptomycin were subsequently administered with disappearance of the spread.

Ultimately all patients in this group of 11 were discharged and they are now classified as inactive.

The use of chemotherapy in pre- and post-operative periods should not be limited to short courses which were administered to the patients in this study. The benefits of delaying surgery while waiting for further improvement under chemotherapy should be carefully weighed against the possibility of development of resistant organisms.

SUMMARY

A five year follow-up of resection in 34 patients for pulmonary tuberculosis is presented.

Twenty-seven (79 per cent) are now classified as inactive.

There were three (9 per cent) post-operative deaths and the same number of re-activations of pulmonary tuberculosis.

RESUMEN

Se presenta el seguimiento de 34 enfermos a quienes se había hecho resección por tuberculosis.

Veintisiete (79 por ciento) se clasifican ahora como inactivos. Hubo tres (9 por ciento) muertes postoperatorias y el mismo número de reactivaciones de tuberculosis pulmonar.

RESUME

L'auteur présente une étude portant sur le contrôle effectué pendant cinq ans sur 34 malades ayant subi une résection pour tuberculose pulmonaire.

27 d'entre eux (79%) doivent maintenant être classés comme stabilisés.

Il y eut trois décès post-opératoires (9%) et le même nombre de rechutes de la tuberculose pulmonaire.

ZUSAMMENFASSUNG

Ergebnisse einer Nachbeobachtung von 34 Patienten fünf Jahre nach Resektionsbehandlung wegen Lungentuberkulose werden vorgelegt.

27 Patienten (79%) sind jetzt als inaktiv zu betrachten. 3 Todesfälle waren zu verzeichnen; 3 weitere Fälle zeigten eine Reaktivierung ihrer Lungentuberkulose.

INTERIM SESSION

The Interim Session of the American College of Chest Physicians will be held at the Benjamin Franklin Hotel, Seattle, Washington, November 25 and 26, 1956. Examinations for Fellowship in the College will be given on Saturday, November 24, under the direction of Dr. Harold G. Trimble, Oakland, California, Chairman of the Board of Examiners. On Monday, November 26, the Board of Regents and Board of Governors will hold their semi-annual meetings at the Benjamin Franklin Hotel and a luncheon will be held for the joint group.

The Clinical Meeting of the American Medical Association will be held in Seattle, November 27-30. Members planning to attend these meetings are requested to write to the Benjamin Franklin Hotel for reservations. Please indicate that you will attend the meeting of the American College of Chest Physicians and give arrival and departure dates.

The Pacific Northwest Chapter of the College will sponsor a scientific program on Sunday, November 25 in the Plaza Room of the Benjamin Franklin Hotel. Dr. Norman Arcese, Seattle, Chairman of the Committee on Scientific Program, has submitted the following preliminary program:

MORNING SESSION

8:00 a.m. Registration

8:30 a.m. "Comfortable Bronchoscopies"
J. Karl Poppe, Portland, Oregon
Discussor: John Tolan, Seattle, Washington

"Pulmonary Cystic Disease: Pre- and Postoperative Function Studies"
Giles Filley, Denver, Colorado
Discussion from the Floor

"The Surgical Treatment of Cavitary and Non-Cavitary Tuberculosis in Non-Infectious Patients"
John W. Bell, Seattle, Washington
Discussor: Thomas Sheehy, Seattle, Washington

"Experiences with a Surgical Procedure for Cor Pulmonale"
William E. VanFleit, Emory University, Georgia
Discussor: Robert Bruce, Seattle, Washington

"Surgical Treatment of Congenital Lung Disease in Children"
Arthur deBoer, Chicago, Illinois
Discussor: Robert Tidwell, Seattle, Washington

"A Critical Evaluation of Intermittent Positive Pressure Breathing Therapy"
Roger H. L. Wilson, San Francisco, California
Discussion from the Floor

"Pulmonary Cytology in Malignant and Non-Malignant Chest Diseases"
Seymour M. Farber, San Francisco, California
Discussion from the Floor

12:15 p.m. Round Table Luncheons

1) "Treatment of Tuberculin Converters"
Chairman: Albert R. Allen, Selah, Washington

2) "Surgical Treatment of Heart Disease"
Chairman: William S. Conklin, Portland, Oregon

3) "Early Diagnosis of Pulmonary Emphysema"
Chairman: Hurley L. Motley, Los Angeles, California

Additional members of round table luncheon panels will be published in the final program.

AFTERNOON SESSION

2:00 p.m. "Wegener's Granulomatosis"
John E. Tuhy, Portland, Oregon
Discussion from the Floor

"Ivalon Graft to Bridge Coronary Artery Occlusions"
Franklin R. Smith, Seattle, Washington

"Lobar Spirometry"
C. J. Martin and Ned Clark, Seattle, Washington
Discussor: Giles Filley, Denver, Colorado

"Studies of Esophageal Intraluminal Pressure: Practical Value in Diagnosis"
Arthur M. Olsen, Rochester, Minnesota
Discussor: Cirus E. Reuben, Seattle, Washington

"Clinical Pathological Correlation of Resected Lung with Tuberculosis with Special Emphasis on the Accuracy of Cavity Prediction"
M. L. Allan and W. G. Trapp, Vancouver, B. C., Canada
Discussor: Richard Greenleaf, Seattle, Washington

3:55 p.m. Chest Disease Conference
Moderator: Herman J. Moersch, Rochester, Minnesota
Panel: John F. Briggs, St. Paul, Minnesota, Edwin R. Levine, Chicago, Illinois and Donald R. McKay, Buffalo, New York

5:00 p.m. Business Meeting, Pacific Northwest Chapter

EVENING SESSION

6:00 p.m. Cocktail Party and Dinner

8:15 p.m. Fireside Conferences

Subjects and Discussion Leaders

"Present Status of Surgery in the Treatment of Coronary Artery Disease"
Franklin R. Smith, Seattle, Washington

"Current Status of Open Cardiac Surgery"
Arthur deBoer, Chicago, Illinois

"Allergy in Bronchopulmonary Disease"
Leon Unger, Chicago, Illinois

"Pulmonary Physiology"
C. J. Martin, Seattle, Washington

"What to do With Unused Beds in Tuberculosis Sanatoria"
Charles K. Petter, Waukegan, Illinois

"Surgery of Aortic Aneurysms"
Luke Hill, Seattle, Washington

"Treatment of Metastatic Carcinoma of the Lung and Pleura" and "Palliative Treatment of Inoperative Pulmonary Malignancy"
Herman J. Moersch, Rochester, Minnesota and J. Thomas Payne, Seattle, Washington

Additional discussion leaders for Fireside Conferences will be published in the final program.

The Fireside Conferences are informal and offer an opportunity for free discussion. Discussion leaders will be seated at tables with proper identification. Physicians may participate in the discussion of their choice, or move on to other discussions when and if they desire.

All physicians are cordially invited to attend the scientific sessions; there is no registration fee.

College Chapter News

JOINT MEETING, POTOMAC AND SOUTHERN CHAPTERS

The Potomac and Southern Chapters will hold a joint meeting at the Shoreham Hotel, Washington, D. C., November 11-12. The following program will be presented:

Sunday, November 11 MORNING SESSION

9:00 a.m. Registration

9:25 a.m. Introductory remarks
Alfred Goldman, St. Louis, Missouri, President, Southern Chapter

9:30 a.m. Scientific Session
William F. Miller, Dallas, Texas, Presiding

"An Evaluation of the Yolk-Sac Method as Compared with Conventional Laboratory Procedures for the Isolation of Mycobacterium Tuberculosis Hominis"
John H. Seabury, Harry E. Dascomb, and Jeanne M. Mottram, B.S., New Orleans, Louisiana

"Pulmonary and Metabolic Aspects of Cystic Fibrosis (Mucoviscidosis)"
Paul A. di Sant'Agnese, New York, New York

"The Current Status of the Pneumonias"
Robert C. Austrian, New York, New York

"The Pathogenesis and Treatment of Peripheral Vascular Collapse Associated with Fulminant Diffuse Pulmonary Infiltrations"
Donald W. Seldin, Dallas, Texas

12:00 noon Luncheon panel discussion: "Physiologic Therapy of Bronchopulmonary Disease"
Alvan L. Barach, New York, New York; Maurice S. Segal, Boston, Massachusetts; William F. Miller, Dallas, Texas, Moderator

AFTERNOON SESSION

1:55 p.m. Introduction
Joseph S. Cruise, Atlanta, Georgia, Second Vice-President, Southern Chapter

2:00 p.m. Edgar W. Davis, Washington, D. C., Presiding

"Application of Hypothermia in the Correction of Cardiovascular Lesions"
Edward J. Jahnke, Jr., Washington, D. C.

"The Clinical Value of Transbronchial Left Heart Catheterization"
L. Biben, A. G. Morrow, H. T. Dodge, and R. P. Grant, Bethesda, Maryland

"Acquired Diseases of the Aorta"
E. Stanley Crawford, Denton A. Cooley, Michael E. DeBakey, and Oscar Creech, Houston, Texas

"Severe Crushing Injuries of the Chest: A New Method of Treatment"
Edward E. Avery, Chicago, Illinois

X-ray Conference
Charles N. Davidson, Baltimore, Maryland, Moderator
Panel: Ross L. McLean, Baltimore, Maryland; Sol. Katz, Washington, D. C., and Otto C. Brantigan, Baltimore, Maryland

EVENING SESSION

6:00 p.m. Cocktail party, sponsored by the Potomac Chapter

7:00 p.m. Banquet—Guest speaker: O. Theron Clagett, Rochester, Minnesota, who will present the Third Paul A. Turner Lecture sponsored by the Southern Chapter entitled "Carcinoma of the Lung"

Monday, November 12 MORNING SESSION

9:00 a.m. Introduction of Edmund G. Beacham, Baltimore, Maryland, President, Potomac Chapter
Roy G. Klepser, Washington, D. C., Vice-President, Potomac Chapter, Presiding

"Features and Significance of Hypertrophic Osteoarthropathy"
James F. Hammarsten and John O'Leary, Oklahoma City, Okla.

"Testing Pulmonary Function in the Doctor's Office and Small Clinic"
James J. Callaway and George R. Meneely, Nashville, Tennessee

"New Concepts of the Epidemiology of Sarcoidosis"
Martin M. Cummings, Edward Dunner, Richard H. Schmidt, Jr., and John B. Barnwell, Washington, D. C.

"Further Observations on the Problem of Mucoid Impaction of the Lung"
Robert R. Shaw, Donald L. Paulson, and John L. Kee, Dallas, Texas

"Ten Years of Tuberculosis Surgery"
J. Maxwell Chamberlain, New York, New York

"Controversial Aspects of the Surgery of Tuberculosis"
James D. Murphy, Baltimore, Maryland

12:00 noon Luncheon and Business Meetings, Potomac and Southern Chapters

All physicians are cordially invited to attend this meeting. There is no registration fee. Those planning to attend the meeting are requested to make hotel reservations through the Housing Bureau of the American College of Chest Physicians, Convention Bureau, 1616 K Street, NW, Washington, D. C.

The Golden Anniversary Meeting of the Southern Medical Association will be held in Washington, D. C., November 12-15.

COLORADO CHAPTER

The Colorado Chapter held its annual meeting at the Stanley Hotel, Estes Park, on September 8. New chapter officers are:

President:	Robert K. Brown, Denver
Vice-President:	Albert Guggenheim, Denver
Secretary-Treasurer:	Leroy Elrick, Denver (re-elected)

ILLINOIS CHAPTER

The Illinois Chapter will hold its first fall meeting on October 18 at the Knickerbocker Hotel, Chicago. This meeting will be held in conjunction with the 11th Annual Postgraduate Course on Diseases of the Chest sponsored by the College. Dr. Burgess L. Gordon, President of the Woman's Medical College, Philadelphia, and President-Elect of the American College of Chest Physicians, will be guest speaker at a dinner at 7:00 p.m. The title of Dr. Gordon's talk will be "Evolution of the Chest Specialist." Following the dinner, at 8:30 p.m., Dr. George R. Meneely, Associate Professor of Medicine, Vanderbilt University School of Medicine, Nashville, will address the Illinois Chapter members and guests on the subject "The Practical Clinical Use of Radioisotopes in the Diagnosis and Treatment of Chest Diseases."

LOUISIANA CHAPTER

The Louisiana chapter will meet in New Orleans on Saturday, October 20. Dr. Oscar Creech, Jr., Assistant Professor of Surgery, Baylor University College of Medicine, Houston, Texas, will speak on cardiovascular surgery, and Dr. John H. Seabury, Professor of Medicine, Louisiana State University School of Medicine, New Orleans, will present a paper on fungus disease. All physicians are cordially invited to attend.

Scientific Program Committee Requests Submittal of Abstracts for 1957 Meeting

The 23rd Annual Meeting of the American College of Chest Physicians will be held at the Hotel Commodore, New York City, May 29 through June 2, 1957. Plans for the scientific program to be presented at this meeting are underway. Emphasis will be placed on papers dealing with new and original research and investigation. One feature of the program will be a session devoted solely to a series of such papers limited to ten minutes for each presentation.

The committee urges those wishing to present papers to submit a 200-word abstract to Dr. Karl H. Pfuetze, Chairman, Committee on Scientific Program, 1919 West Taylor Street, Chicago, Illinois, before December 1, 1956.

1957 Prize Essay Contest

The 1957 Prize Essay Contest, sponsored by the Council on Undergraduate Medical Education of the College, is open to undergraduate medical students throughout the world. This year, the awards have been increased to $500 for first prize, $300 for second prize, and $200 for third prize. Winners will also receive certificates of merit.

The Board of Regents of the College requests the cooperation of College members affiliated with medical schools in bringing the contest to the attention of the student body at their respective schools. Essays may relate to the diagnosis and/or treatment of cardiac or pulmonary diseases. The contest will close on April 10, 1957 and instructions for the preparation of manuscripts are as follows:

1) Five copies of the manuscript, typewritten in English, double spaced, should be submitted to the Committee on College Essay, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.
2) The only means of identification of the author shall be a motto or other device on the title page and a sealed envelope bearing the same motto on the outside, enclosing the name and address of the author.
3) A letter from the dean or chairman of the department of medicine or surgery of the medical school, certifying that the author is an undergraduate student.

Dr. Schwartz Elected President, Bronx County Medical Society

Dr. George Schwartz, New York City, has been elected President of the Bronx County Medical Society and will be officially installed at a dinner at the Concourse Plaza Hotel on October 17, 1956. Following the dinner, the Ambassador from Viet Nam, the Hon. Tran Van Chuong, will address a meeting of the society. Members of the College are cordially invited to hear the Ambassador's talk commencing at 9 p.m.

Postgraduate Courses in Pediatric Cardiology

Three intensive postgraduate courses in Pediatric Cardiology, under the direction of Drs. Benjamin M. Gasul and Egbert H. Fell, are scheduled to be offered during the two weeks beginning November 5, 1956, at the Cook County Graduate School of Medicine, Chicago. They will include a one week course in the Diagnosis and Treatment of Congenital and Rheumatic Heart Disease, two courses of three days each in Roentgenology and Electrocardiography in Heart Disease, and in Angiocardiography and Catheterization of the Heart and Great Vessels. The courses, designed for pediatricians, roentgenologists and internists, will be didactic and clinical, and will utilize an abundance of interesting clinical cases and case histories. Registration for each course will be limited and will be considered in the order received. For further information write to the Registrar, 707 South Wood Street, Chicago 12, Illinois.

MEDICAL SERVICE BUREAU

POSITIONS WANTED

F.C.C.P., age 40, with wide experience, desires medical chest location, preferably with maintenance for large family. Now licensed in California, but will consider midwest or east. Please address inquiries to Box 285B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Chest surgeon, 58, desires post in sanatorium, west coast preferred. 25 years experience in sanatoria as physician and surgeon; 7 years special training in thoracic surgery. F.A.C.S., Diplomate, national board, California license. Please address inquiries to Box 286B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois

POSITIONS AVAILABLE

Young physicians wanted at 500-bed hospital for chest diseases; active medical, surgical, training, and research programs. Salary range $7,570 to $13,760. Write or apply: Manager, VA Hospital, San Fernando, California.

Assistant medical director wanted for Mineral Springs Sanatorium, Cannon Falls, Minnesota, a 100-bed county tuberculosis hospital with active medical, surgical, out-patient, and investigative programs. Salary determined by experience. Furnished house and utilities supplied. Applicant must be male graduate of approved U. S. or Canadian medical school and eligible for Minnesota license. Address: E. V. Bridge, M.D., Superintendent.

Staff physician wanted for surgical service of 256-bed VA tuberculosis hospital. Thoracic surgery experience preferred but general surgeon desiring thoracic surgical training acceptable. Staff salaries $7570-$12,675 depending on qualifications. U. S. license and citizenship required. Write: Manager, VA Hospital, Waukesha, Wisconsin.

Full-time **staff physician** wanted for the Idaho State Tuberculosis Hospital, Gooding, Idaho. New, fully modern hospital building nearing completion to replace several small, antiquated units, bringing the total bed capacity to 100-120 beds. Salary governed by training and experience. Apply: Medical Director, Idaho State Tuberculosis Hospital, Gooding, Idaho.

For Sale: Fully equipped private practice of recently deceased internist, specializing in diseases of the chest and cardiology, in progressive city near Pittsburgh, Pennsylvania. Opportunities excellent in either field for accredited man. Reasonable. Please forward inquiries to Box 288A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

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